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## Metabolic (dysfunction)-associated fatty liver disease in individuals of normal weight

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**Abstract** | Metabolic (dysfunction)-associated fatty liver disease (MAFLD) affects up to a third of the global population; its burden has grown in parallel with rising rates of type 2 diabetes mellitus and obesity. MAFLD increases the risk of end-stage liver disease, hepatocellular carcinoma, death and liver transplantation and has extrahepatic consequences, including cardiometabolic disease and cancers. Although typically associated with obesity, there is accumulating evidence that not all people with overweight or obesity develop fatty liver disease. On the other hand, a considerable proportion of patients with MAFLD are of normal weight, indicating the importance of metabolic health in the pathogenesis of the disease regardless of body mass index. The clinical profile, natural history and pathophysiology of patients with so-called lean MAFLD are not well characterized. In this Review, we provide epidemiological data on this group of patients and consider overall metabolic health and metabolic adaptation as a framework to best explain the pathogenesis of MAFLD and its heterogeneity in individuals of normal weight and in those who are above normal weight. This framework provides a conceptual schema for interrogating the MAFLD phenotype in individuals of normal weight that can translate to novel approaches for diagnosis and patient care.

Metabolic dysfunction-associated fatty liver disease (MAFLD) refers to steatosis and potentially severe lesions of steatohepatitis and associated fibrosis. It develops in the context of an unhealthy metabolic milieu, most notably overweight or obesity, and is associated with disturbances of glucose homeostasis and lipid handling. MAFLD is not just a liver disease but rather one component of a multifaceted, multi-organ collection of diseases driven by complex gene–environment interactions resulting in a dysfunctional metabolic milieu with diverse effects<sup>1</sup>.

MAFLD is a leading cause of end-stage liver disease, liver cancer and liver transplantation. It is the sole cause of chronic liver disease in about 20–30% of the global population and a component of liver disease in up to 50%<sup>2–4</sup>. An estimated 20 million people per year will likely die from fatty liver disease worldwide<sup>2–4</sup>. According to the Global Burden of Disease data set, MAFLD is the fastest-growing cause of cirrhosis, liver failure and liver cancers<sup>5</sup>. As expected, MAFLD imposes a major economic burden on society and reduces the health-related quality of life of affected patients<sup>6</sup>.

The prevalence of MAFLD has been increasing for the past few decades as a function of increasing incidence, longer disease duration and an ageing population, all within the context of an obesogenic environment favouring the consumption of high-calorie foods and physical inactivity<sup>7,8</sup>. However, not everyone exposed to this environment gains weight or develops MAFLD and, similarly, not everyone with MAFLD has obesity. Despite advances in our understanding of MAFLD pathogenesis, a remaining challenge is to develop a better understanding of the heterogeneity of the disease<sup>9,10</sup>. This challenge is no better exemplified than when it comes to understanding the pathophysiology of fatty liver

disease that develops in individuals within the normal body mass index (BMI) category (BMI 18.5–24.9 kg/m<sup>2</sup>), which, in this Review, we refer to as individuals of normal weight. Despite having a normal BMI, the vast majority of these patients are not metabolically healthy and can be considered to have MAFLD, referred to in this Review as individuals with lean MAFLD. Can we define this group of patients better than using BMI and the presence of excess liver fat? Furthermore, which measures and thresholds of overweight and obesity or metabolic dysregulation best define these individuals? Cross-sectional studies have described the pathophysiological features and some aspects of the natural history of fatty liver disease in individuals of normal weight<sup>11</sup>. However, this has yet to be translated to inform management rigorously. Although new treatments are being developed for patients with non-lean fatty liver disease, there is no clarity on pharmacotherapies for lean MAFLD<sup>12</sup>. Whereas typical risk factors, such as insulin resistance, are present in most patients with overweight or obesity, their relative contributions and associations are less well defined in patients of normal weight despite both groups having a similar natural history, including liver-related events and overall mortality<sup>13</sup>. Thus, the diagnosis and treatment of patients with lean MAFLD pose challenges with many open questions.

In this Review, we summarize knowledge about lean MAFLD and provide perspectives on current concepts of metabolic health and metabolic flexibility as a basis to better understand the biology and natural history of this disease and to provide pointers on likely therapies (Box 1). There is a marked overlap between nonalcoholic fatty liver disease (NAFLD) as previously defined and MAFLD<sup>14,15</sup>, and based on a Cohen kappa value of up to 0.92, the overall concordance of the two definitions is high<sup>16</sup>. In addition, a meta-analysis including data from 17 studies that comprised 9,808,677 individuals worldwide showed that the prevalence of MAFLD was comparable to that of NAFLD. Only 4.0% of patients with NAFLD did not meet the novel MAFLD diagnostic criteria<sup>17</sup>. According to the proposed criteria, MAFLD is diagnosed when patients with hepatic steatosis meet at least one of the following three criteria: overweight or obesity, type 2 diabetes mellitus (T2DM), or evidence of metabolic dysregulation if they are of normal weight. Current evidence also indicates that the MAFLD diagnostic criteria are more accurate than NAFLD for predicting disease progression in population-based studies and predicting hepatic and extrahepatic outcomes such as cardiovascular disease, chronic kidney disease, impairment of lung function and cognitive impairment<sup>18–23</sup>. As is discussed here, the concept has even more utility when trying to understand the pathophysiology of fatty liver disease in people of normal weight, for whom the overarching conceptual schema of metabolic dysregulation becomes even more critical than in people with obesity. Therefore, in this Review, we use the term MAFLD with appropriate clarifications where necessary.

## **Current definition of lean MAFLD**

Standard definitions of overweight and obesity are based on BMI using ethnicity-specific cut-offs. Among those of European descent, an adult BMI of 25–29.9 kg/m<sup>2</sup> is considered overweight, a BMI of ≥30 kg/m<sup>2</sup> is considered obesity (class 1, BMI of 30 to <35; class 2, BMI of 35 to <40; class 3, also categorized as ‘severe’ obesity, BMI of 40 or higher) and a BMI of 18.5–24.9 kg/m<sup>2</sup> is considered normal weight (that is, lean)<sup>24</sup>. In Asian populations, a BMI of 23.0–24.9 kg/m<sup>2</sup> is considered overweight, a BMI of ≥25.0 kg/m<sup>2</sup> is considered obesity and a BMI of 18.5–22.9 kg/m<sup>2</sup> is considered normal weight<sup>25</sup>. According to the international consensus recommendation for the definition of MAFLD, patients with hepatic steatosis and overweight or obesity are considered to

have MAFLD whereas, for a diagnosis of MAFLD with normal weight (that is, lean MAFLD), both hepatic steatosis and evidence of metabolic dysregulation (the presence of at least two risk factors amongst increased waist circumference, hypertension, low serum high-density lipoprotein (HDL)-cholesterol levels, hypertriglyceridaemia, impaired fasting plasma glucose, insulin resistance and chronic subclinical inflammation) must be present<sup>9,12,14</sup>.

## **Clinical characteristics of lean MAFLD Epidemiology**

For the reasons discussed earlier and for consistency, in discussing epidemiology, we use the term MAFLD. However, all studies performed so far were undertaken before the publication of the international consensus definition<sup>14</sup>. One of the first studies to estimate the prevalence of lean MAFLD was conducted in South Korea in 2004 among 932 community-based people without T2DM who were negative for hepatitis C and/or hepatitis B virus and had an alcohol intake of more than 140 g per week<sup>26</sup>. In this study, fatty liver seen via liver ultrasonography was reported in 23.4% of participants, and 16.1% of the population of normal weight (defined as a BMI of 18.5 to <25 kg/m<sup>2</sup>, using the European rather than the Asian BMI cut-off) was associated with evidence of metabolic dysregulation<sup>26</sup>. Subsequently, MAFLD in individuals of normal weight has been described in several populations worldwide with a prevalence that varies widely (between 5% and 26%) and constitutes 15–50% of cases with MAFLD (Fig. 1 and Supplementary Table 1). For example, in a study of 810 Chinese individuals of normal weight, the prevalence of MAFLD was 17.5%<sup>27</sup>. Another study of 911 individuals from the general population in Hong Kong demonstrated that the prevalence of MAFLD was 19.3% among individuals without T2DM<sup>28</sup>.

Most of the studies discussed earlier reported on NAFLD prevalence (that is, without using the MAFLD criteria) and, therefore, excluded people with viral hepatitis. Additionally, they used various definitions of alcohol use to diagnose NAFLD and did not exclude other diseases, such as Wilson disease or haemochromatosis, as required by the NAFLD definition<sup>15</sup>. Thus, it is likely that studies conducted under NAFLD criteria underestimated MAFLD in individuals of normal weight since MAFLD criteria assume that multiple aetiologies can exist in the same person whereas the definition of NAFLD is exclusionary. Studies variably report on one or more of three possible types of prevalence estimates in individuals of normal weight: one is an overall (or global) prevalence, which pertains to the proportion of people with lean MAFLD in the overall examined population; the second is the prevalence of lean MAFLD as a proportion of people of normal weight; and the third is the prevalence of lean MAFLD as a proportion of all people with any MAFLD. For example, if 10 people with MAFLD (of whom 5 are of normal weight) are found in an underlying overall population of 100 (of whom 50 are of normal weight), then the overall prevalence of lean MAFLD is 5%, the prevalence of MAFLD in individuals of normal weight is 10% and the prevalence of lean MAFLD in the overall MAFLD population is 50%. At least four systematic reviews with meta-analyses estimated the prevalence of fatty liver disease in individuals of normal weight<sup>29–32</sup>. Given the high concordance between NAFLD and MAFLD, the data can be considered representative of MAFLD, with each report highlighting some aspect of MAFLD epidemiology in persons of normal weight. A meta-analysis that included 93 separate reports and was published in May 2020 reported that the overall lean MAFLD prevalence was 5.1% (95% CI 3.7–7.0) and the prevalence of lean MAFLD in the global MAFLD population was 19.2%<sup>29</sup> (95% CI 15.9–23.0). A meta-analysis of Japanese studies published in February 2021 pooled individual patient-level data

from 14,887 patients and reported a 20.7% prevalence of lean MAFLD in the overall MAFLD population; persons with lean MAFLD were older than the rest of patients with MAFLD (median age for patients with lean MAFLD 60 versus 58 and 52 years for patients with MAFLD and with overweight or obesity, respectively;  $P < 0.001$ )<sup>30</sup>. A meta-analysis of studies published in May 2020 reported a pooled prevalence of 11.2% (95% CI 9.6–13.0) of MAFLD in the lean population from 30 studies and of 9.2% (95% CI 7.4–11.3) from 15 studies with a sample size equal to or greater than 1,000 study participants<sup>31</sup>. The prevalence of MAFLD in the lean population was 12% in Asia, 10.2% in the Middle East and 9.2% in Europe.

Individuals with lean MAFLD had higher odds for metabolic syndrome and its components, for the patatin-like phospholipase domain-containing protein 3 (PNPLA3) G allele, and an inflammatory profile including elevated uric acid and C-reactive protein levels in serum. A meta-analysis of 33 observational studies published in December 2020 reported a similar overall prevalence of lean MAFLD of 4.1% (95% CI 3.4–4.8) but with higher estimates from studies conducted in China, India, Korea, Malaysia, Japan, Bangladesh and Sri Lanka (4.8%; 95% CI 4.0–5.6) and lower estimates from studies conducted in Europe (2.2%; 95% CI 2.3–3.8)<sup>32</sup>. This meta-analysis also reported the prevalence of lean MAFLD, showing an upward trend between 1988 and 2017. Similar to MAFLD overall, MAFLD prevalence among individuals of normal weight was characterized by considerable racial and ethnic variations, with US-based studies showing higher prevalence in people with heritage from Latin America and lower prevalence in African Americans<sup>33,34</sup>.

Considerably fewer data are available about the incidence of MAFLD among individuals of normal weight. The incidence in the non-obese population (BMI  $<30$  kg/m<sup>2</sup> for the non-Asian and BMI  $\leq 27.5$  kg/m<sup>2</sup> for the Asian population) was pooled from five studies and was reported to be 24.6 (95% CI 13.4–39.2) per 1,000 person-years<sup>29</sup>.

As evident from these data, there are limitations in our current knowledge of the epidemiology of patients with lean MAFLD. The variations among studies are likely attributed to the lack of a widely accepted definition of the so-called lean fatty liver disease<sup>29–32</sup> that reflects its pathophysiology, the poor performance of diagnostic modalities to identify the presence of liver fat (typically via ultrasonography) at the population level, the heterogeneity of diagnostic criteria used in individual reports and different study participant selection criteria.

## **Histological characteristics**

Morphologic features of MAFLD in individuals of normal weight are thought to be indistinguishable from the rest of MAFLD, including in the subset of patients showing features of steatohepatitis with or without fibrosis<sup>11</sup>. Several cross-sectional studies indicated that patients with lean MAFLD had a better histological and metabolic profile than patients with obesity. A study of 1,339 patients with biopsy-proven fatty liver from four territories (Italy, UK, Spain and Australia) reported that patients of normal weight, as defined by BMI, had histologically less severe disease (steatohepatitis in 54.1% versus 71.2%; advanced fibrosis in 10.1% versus 25.2%) and a lower prevalence of T2DM (9.2% versus 31.4%) than patients with overweight<sup>13</sup>. Similar findings were reported in a study of 3,386 patients with lean MAFLD from the USA, where patients of normal weight had a significantly lower prevalence of metabolic abnormalities (diabetes: 32.6% versus 53.5% of non-lean participants; hypertension: 47.8% versus 67.4% of non-lean participants; dyslipidaemia: 54.0% versus 64.1% of non-lean participants), cirrhosis (22.6% versus 40.2% of non-lean participants) and cardiovascular disease (9.0% versus 14.8% of non-lean participants;  $P < 0.0001$  for all comparisons) than those without normal weight accord-

ing to BMI<sup>35</sup>. A study from India showed that participants with BMI greater than or less than 25 kg/m<sup>2</sup> (not the accepted BMI criteria for Asian populations) had the same degree of liver injury<sup>36</sup>. Another meta-analysis of 8 studies including 1,441 persons reported that 39% of those with lean MALFD had steatohepatitis and 29.2% had clinically significant fibrosis more or equal to stage 2 compared with individuals with obesity and MAFLD (52.9% and 38.3%, respectively)<sup>29</sup>. It should be noted, however, that other cross-sectional studies have reported worse liver histology in patients with lean MAFLD with higher proportions of advanced fibrosis, ballooning and lobular inflammation as well as greater steatohepatitis than patients with non-lean MAFLD<sup>37,38</sup>.

## Prognosis

Data on the long-term prognosis of MAFLD in individuals of normal weight is scarce and conflicting. A study conducted in 2014, including 483 patients with biopsy-proven MAFLD with a median follow-up of 11 years, demonstrated a higher liver transplantation rate in those with normal weight than in those with obesity<sup>39</sup>.

Similarly, a study of 646 Swedish patients (n = 123 with BMI <25 kg/m<sup>2</sup>, n = 335 with BMI 25–29.9 kg/m<sup>2</sup> and n = 188 with BMI >30 kg/m<sup>2</sup>) with biopsy-proven MAFLD and a median of 19.9 years of follow-up, reported a 2.69-fold increased risk for development and progression to severe liver disease compared with patients with obesity and MAFLD but no increase in mortality in patients of normal weight<sup>40</sup>. A study including 1,339 patients with biopsy-proven MAFLD with a median follow-up of 94 months also showed no difference in survival compared with patients with non-lean MAFLD<sup>13</sup>. A meta-analysis of 3 studies including a total of 35,707 persons showed that the overall, liver-specific and cardiovascular-specific mortality rates were 12.1, 4.1 and 4 per 1,000 person-years, respectively, in patients with lean MAFLD. By contrast, the rates were 7.5, 2.4 and 2.4 per 1,000 person-years, respectively, among patients with obesity and MAFLD<sup>29</sup>. Another meta-analysis of 4,307 patients with MAFLD from two cohorts showed that patients with lean MAFLD had higher all-cause mortality than patients with non-lean MAFLD (8.3 versus 5.6 per 1,000 person-years, respectively; cut-offs were BMI <23 kg/m<sup>2</sup> as normal weight; BMI 23–27.5 kg/m<sup>2</sup> as overweight and BMI >27.5 kg/m<sup>2</sup> as obesity)<sup>30</sup>. However, a few other reports suggested that clinical events and prognosis were worse, with higher cardiovascular events and death, in patients with obesity than in patients of normal weight within the MAFLD population<sup>41,42</sup>.

MAFLD in individuals of normal weight is associated with an increased risk of several extrahepatic manifestations<sup>43</sup>. For example, a longitudinal study of 14,482 Chinese adults (n = 7,898 men and n = 6,584 women) with euglycaemia and without T2DM who participated in a health check-up programme reported that, over a median of 6.0 years of follow-up, MAFLD in individuals of normal weight was a significant risk factor for incident T2DM in both sexes (P < 0.001)<sup>43</sup>.

The adjusted hazard ratio (aHR) (95% CI) for incident T2DM in patients with lean MAFLD versus individuals of normal weight and without MAFLD was 2.58 (95% CI 1.68–3.97) and the effect appeared more pronounced in women<sup>43</sup>. Notably, the relative risk of developing T2DM was similar between individuals of normal weight with MAFLD and those with overweight or obesity and MAFLD both in the entire study population and in subgroups stratified by sex<sup>43</sup>. Conversely, in a longitudinal study on patients of European descent with MAFLD with more than 10,483 person-years, T2DM occurred in 90 of 785 patients without normal weight (BMI ≥25 kg/m<sup>2</sup>) versus in 11 of 177 patients of normal weight (BMI <25 kg/m<sup>2</sup>) (aHR 1.55, 95% CI 0.83–2.9; P = 0.171) and cardiovascular events occurred in

122 of 1,083 patients without normal weight versus in 14 of 192 patients of normal weight (aHR 1.3, 95% CI 0.73–2.2; P = 0.39)<sup>13</sup>.

Real-world data from 4,711 patients with MAFLD suggested that patients with lean MAFLD might have greater 15-year cumulative all-cause mortality but no difference in cardiovascular or cancer-related mortality compared with patients with obesity and MAFLD<sup>44</sup>.

Sub-analysis of data from the National Health and Nutrition Survey III also indicated that patients with lean MAFLD experienced significantly greater all-cause (P = 0.0002) and cardiovascular mortality (P = 0.0004) than individuals of normal weight and without MAFLD, although it was lower than in patients with non-lean MAFLD<sup>45</sup>. By contrast, some other reports demonstrated that patients with lean MAFLD had a lower prevalence of T2DM, hypertension, dyslipidaemia and cardiovascular disease than patients with non-lean MAFLD<sup>11,35</sup>.

In summary, patients with lean MAFLD had a worse long-term outcome than healthy individuals and might have a similar prognosis to patients with overweight or obesity and with MAFLD (Fig. 2). Adverse liver-related outcomes in patients with lean MAFLD might not appropriately explain the all-cause mortality. The apparent contradiction of increased liver-related morbidity and mortality in patients of normal weight with less severe baseline liver damage might be explained by heterogeneity in study design as well as by management difficulties in the absence of overt risk factors to be targeted such as obesity<sup>46</sup>. In addition, some of the variation in evidence might relate to the so-called obesity paradox or to misclassification bias; for example, using BMI as a measure of adiposity, reverse causation in short-term studies (in cross-sectional studies or studies with a short duration of follow-up of 1–2 years), a form of selection bias (collider stratification), or the presence of other unmeasured or poorly accounted for confounders, such as alterations of other aspects of metabolic health<sup>47,48</sup>.

Ultimately, rigorous studies, especially those conducted prospectively in large representative cohorts based on a robust definition that stems from a better understanding of pathophysiology rather than on BMI, will be required.

### **Pathophysiology of lean MAFLD Genetic contribution**

The variation in MAFLD risk within a shared environment and the way people respond to these environmental cues is partly determined by their genetic profile<sup>49,50</sup>.

Typically, the genetic contribution is calculated by heritability, a population-level estimate of the extent of variation in disease susceptibility that is attributable to genetic variation. The heritability of MAFLD was estimated, in twin studies, to be 50%<sup>51</sup>. Despite the success of genome-wide association studies (GWAS) in identifying gene loci associated with the risk of MAFLD development and progression, pinpointing the variants associated in patients with lean MAFLD remains elusive<sup>52</sup>.

A GWAS of 1,275 Japanese patients with fatty liver disease and of normal weight, compared with 1,411 healthy individuals adjusted for age, sex and alcohol consumption, suggested human leukocyte antigen as a candidate locus associated with fatty liver susceptibility in patients of normal weight that might be influenced by alterations in the gut microbiota<sup>53</sup>. Another whole-exome sequencing study in a small cohort of 6 patients of Indian descent with lean MAFLD and 2 healthy individuals, which was replicated in a validation cohort of 191 patients with lean MAFLD and 105 healthy individuals, implicated a variant in phosphatidylethanolamine N-methyltransferase in lean MAFLD<sup>54</sup>. However, these findings need to be validated in larger populations as well as in other ethnicities. Other studies have investigated the role of previously identified MAFLD variants in the lean subgroup

of patients. For example, the allele frequency of rs738409 C>G, encoding PNPLA3<sub>I148M</sub>, the most validated variant for MAFLD, seemed to be higher in Hong Kong patients with lean MAFLD than in those with obesity and MAFLD. However, in a study of patients of European descent with lean MAFLD, no statistically significant difference in the risk allele frequency was observed<sup>28,55</sup>. Several other reports demonstrated independent associations of the PNPLA3 risk allele with steatohepatitis development and higher stages of fibrosis (stage 2 or more) in patients of normal weight with MAFLD<sup>13,28,55</sup>.

Studies comparing patients with MAFLD who are of normal weight to patients with obesity (as per BMI categories) reported higher rates of carriage of the rs58542926 C>T in the transmembrane 6 superfamily member 2 (TM6SF2) locus, which is robustly implicated in MAFLD<sup>56,57</sup>, in patients with lean MAFLD<sup>38,55</sup>. Membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) rs641738 C>T is another variant associated with the risk of MAFLD, hepatic inflammation and fibrosis (including non-MAFLD liver disease) as well as the risk of progression to hepatocellular carcinoma<sup>58,59</sup>. However, in another report, carriage of the MBOAT7 rs641738 C>T allele was not statistically significantly different between patients of normal weight with MAFLD (n = 74, BMI  $\leq 25$  kg/m<sup>2</sup>) and patients with overweight (n = 242, BMI 25–30 kg/m<sup>2</sup>) or obesity (n = 150, BMI >30 kg/m<sup>2</sup>) and MAFLD<sup>37</sup>. Lastly, interferon  $\lambda 3/4$  variants, initially implicated in liver injury and fibrosis progression in patients chronically infected with hepatitis C virus, were demonstrated to be associated with fibrosis severity in patients with MAFLD, with a more profound effect in patients of normal weight. The independent association between rs368234815 TT and severe fibrosis was significant in patients of normal weight (OR 1.81, 95% CI 1.11–3.07; P = 0.02) but not in patients with obesity (OR 1.49, 95% CI 0.87–2.61; P = 0.15)<sup>60–62</sup>.

The human epigenome provides pivotal insights for understanding the basis of gene–environment interactions that are likely to be implicated in the pathogenesis of MAFLD in people of normal weight, though it is not well explored. In this context, as epigenetics demonstrates high plasticity to diet and stress, an unfavourable intrauterine environment can induce fetal metabolic programming that increased the risk of MAFLD in adulthood<sup>49</sup>.

Intrauterine growth retardation was associated with more severe insulin resistance and disease activity on histology, independently of BMI<sup>63</sup>, in 90 children with MAFLD. At an average age of 11 years, most children with fatty liver (80%) born small for gestational age were insulin resistant despite a normal BMI and a low prevalence of metabolic abnormalities<sup>63</sup>.

## Metabolic health

Although the pathophysiology of MAFLD in individuals of normal weight is still not clear, metabolic dysregulation is likely the key determinant<sup>11,64</sup>. Currently, there is no consensus among scientists or clinicians about the parameters and cut-off values to define metabolic health and more than 30 definitions have been proposed<sup>65</sup>. Broadly, at the clinical level, metabolic health can be defined as the absence of cardiometabolic disease or risk factors that portend the future development of such disease. In the context of the clinical algorithms currently used, most studies use a definition of having less than two metabolic syndrome criteria to define metabolic health<sup>3,66,67</sup>. However, these definitions pertain to the late manifestation of metabolic dysregulation. By contrast, strict physiological criteria likely identify metabolic dysfunction at an earlier stage, though the tests required, such as the euglycaemic clamp technique, are not suitable for clinical practice or for population-based studies.

As proposed by Smith and Kahn physiological measures of metabolic health include accurate assessment of intrahepatic lipid accumulation and measures of insulin sensitivity<sup>68</sup>. If we adopt this concept, all patients of normal weight with MAFLD will likely have metabolic dysregulation. As an example, in a cohort of 12 patients with biopsy-proven MAFLD without T2DM, obesity and metabolic



syndrome, the observed metabolic profile of insulin resistance in the key target tissues (muscle, liver and adipose tissue) was not distinct from that in obesity<sup>69</sup>. Thus, insulin resistance in adipose tissue represents a key site even in the context of a low BMI and normal-weight subcutaneous fat depots<sup>69</sup>. It was reported that up to 30% of individuals of normal weight demonstrated cardiometabolic risk factors and were termed as metabolically obese normal weight or metabolically unhealthy normal weight<sup>70,71</sup>. Metabolically unhealthy individuals were at high risk of MAFLD irrespective of BMI<sup>11</sup>. The highest risk for steatohepatitis development and fibrosis progression also occurred among the group considered to be metabolically unhealthy, irrespective of BMI (n = 226 patients of normal weight and n = 595 patients with obesity)<sup>72</sup>. Similarly, the risk for cardiovascular disease among individuals with metabolically unhealthy normal weight was approximately 1.5–3-fold higher than among metabolically healthy individuals of normal weight (n = 119)<sup>73,74</sup>. In addition, it can be postulated that the observed substantial geographic and ethnic variation in the prevalence of patients with lean MAFLD might be attributed to a differential prevalence of metabolic health between these regions or populations (that is, Asia, Europe and Latin America). In the Multi-Ethnic Study of Atherosclerosis, the prevalence of patients of normal weight who were metabolically unhealthy ranged from 21% in individuals of European descent (n = 2,622), 32% in Chinese Americans (n = 803), 31% in African Americans (n = 1,893), 38.5% in Latinx individuals (n = 1,496) and 43.6% in South Asian individuals (n = 803). In the same study, the prevalence of lean MAFLD (BMI <30 kg/m<sup>2</sup>) assessed by computed tomography scan was 11%, including 9% among individuals of European descent, 6% among African Americans and 18% among Latinx individuals<sup>75</sup>. However, additional studies using a rigorous definition are required to better understand these differences.

In cross-sectional studies of patients with MAFLD, those with lean disease (n = 99) had a more favourable metabolic profile than those with overweight and obesity (n = 439)<sup>11</sup>. Whether this point towards variation in the sensitivity of metabolic dysfunction to predict future MAFLD risk across the BMI range is a reflection of the imprecise criteria used to define metabolic health in clinical studies needs to be explored. The former would mandate developing BMI-specific criteria for metabolic health. Either way, it suggests that consideration of metabolic health is crucial when assessing for MAFLD risk in individuals of normal weight<sup>14,64</sup>. Notably, according to the findings of the Emerging Risk Factor Collaboration, the associations between hyperglycaemia<sup>76</sup> and blood lipid levels<sup>77</sup> with cardiovascular disease risk were generally not modified by BMI. The same was demonstrated for waist circumference and waist-to-hip ratio, although the risk gradients seemed to be more prominent for individuals of normal weight than in those with obesity (n = 221,934 in total)<sup>78</sup>. Thus, as there is limited evidence to show that risk factors are overall different for people of normal weight compared with individuals with overweight and obesity, risk factors used to define metabolic health are useful for quantifying risk in the absence of detailed and cumbersome physiological studies.

Another problem when applying BMI as a metric is an implicit assumption that BMI is a surrogate for adiposity. Although BMI is a valuable tool that can approximate overall body fat for epidemiology surveillance and daily practice, it fails to capture other metabolically relevant aspects of adiposity, particularly differences in body fat distribution and function. This assumption led to a considerable disparity in health outcomes between individuals with similar BMI<sup>79,80</sup>.

It is now well recognized that the location and subtype of adipose tissue used to store excess calories are more important for metabolic health-related outcomes than overall BMI<sup>79,80</sup>. Measures of central obesity, such as waist circumference and waist-to-hip ratio, better predicted the risk of cardiovascular events than BMI, although this might differ across populations<sup>81</sup>. Even though the latter suggests that waist circumference would be a useful parameter to stratify individuals with obesity as metabolically

healthy or unhealthy and would more precisely enable the identification of individuals at cardiometabolic risk as compared with BMI, the additional relative contribution of adiposity to overall risk prediction (after accounting for traditional risk factors) is only modest. This modest risk prediction is likely, in part, a result of the strong collinearity between BMI and waist circumference, with the vast majority of individuals with a BMI in the obese range also having a large waist circumference<sup>82</sup>. Furthermore, waist circumference did not accurately or consistently, depending on the racial or ethnic group, reflect the relative distribution of visceral abdominal fat, which accounted for only 7–15% of total body fat but had a more important role than subcutaneous fat in the pathogenesis of insulin resistance<sup>83,84</sup>.

Notably, the contribution of adiposity measures (for example, BMI and waist circumference) was substantially smaller than that derived from information on metabolic risk factor levels<sup>78</sup>. This observation was not surprising because risk factors were the outcome of long-term metabolic dysfunction<sup>82</sup>. However, in individuals with lean MAFLD, waist circumference might be a more informative tool to define metabolic health than BMI. Identifying alternative measures of body fat, and specifically measures of fat distribution that can be easily used in clinical practice, and other cardiometabolic risk markers (for example, high sensitivity C-reactive protein) for determining metabolic health is required<sup>74</sup>.

Last but not least, the BMI value does not inform on body composition, that is, fat versus muscle mass<sup>47,85</sup>. Sarcopenia, defined as a progressive and generalized loss of skeletal muscle mass, strength and function, is an important risk factor for the development of MAFLD independent of BMI<sup>86,87</sup>.

### ***What mechanisms predispose to metabolically unhealthy phenotypes?***

The precise mechanisms responsible for preserved or altered metabolic health are not fully understood. A multitude of factors, including genetics, epigenetics, alcohol intake, lifestyle factors such as diet quantity and quality, physical activity, the enterohepatic circulation and gut microbiota, likely interact in a complex and dynamic manner to shape an individual's metabolic health status and consequently the risk of MAFLD<sup>9,52</sup> (Fig. 3).

There is limited knowledge on the role of lifestyle factors, such as diet quality and physical activity, in determining metabolic health in individuals of normal weight. However, the high prevalence of metabolic abnormalities in patients with lean MAFLD suggests that, apart from an overall caloric load, diet quality might be one of the independent determinants of metabolic health<sup>8</sup>. For example, pro-inflammatory diets or dietary patterns with a higher pro-inflammatory profile were implicated in determining metabolic health<sup>88</sup>. A study (n = 4,786) demonstrated that components of dietary intake, including high intakes of sugar and low intakes of cereals, fish and root vegetables, were associated with normal weight obesity, a phenotype with a high body fat percentage and poor metabolic health<sup>88</sup>. Another study reported that individuals of normal weight and with so-called metabolic obesity (n = 30) consumed higher total energy, less fibre, lower amounts of antioxidant compounds and fewer servings of fruit, legumes, nuts and seeds compared with healthy individuals of normal weight (n = 30)<sup>89</sup>. Notably, it was reported that cholesterol intake was higher in patients with lean MAFLD than in patients with obesity and MAFLD<sup>90–92</sup>. It should be noted that another study found differences in physical fitness but not in diet quality among individuals of normal weight and with metabolic obesity (n = 164) compared with healthy individuals of normal weight (n = 100)<sup>93</sup>. The Dietary Inflammatory Index is a dietary tool that was developed to evaluate the overall inflammatory potential of a person's diet<sup>94</sup>, and studies showed a positive correlation between higher Dietary Inflammatory Index scores

and serum inflammatory markers (such as C-reactive protein)<sup>95</sup>. Diet also exerts a dominant effect on microbiota composition irrespective of the host genotype<sup>96</sup>. The possible influence of the gut microbiome on metabolic health and MAFLD is a rapidly emerging area of research. For example, a study found that patients with lean MAFLD (n = 5) might have a gut microbiota profile that is distinct from that of patients with obesity and MAFLD (n = 24), with enrichment of microbiota implicated in the generation of hepatic steatosis (such as Erysipelotrichaceae and Clostridiales)<sup>11</sup>. Analysis of microbiota demonstrated a distinct separation in profiles between healthy individuals of normal weight and individuals with lean MAFLD; in the lean MAFLD group, there was an increased abundance of the Dorea spp. and a reduction in the relative abundance of several species, including Marvinbryantia and the Christensenellaceae R7 group<sup>11</sup>. Emerging evidence also supports the role of differences in total fat mass and regional fat accumulation in shaping a metabolically healthy versus unhealthy phenotype<sup>97</sup>. According to this hypothesis, the limited storage capacity of peripheral adipose tissues, such as the subcutaneous adipose tissue (SAT) that has a minimal metabolic effect, in the context of overnutrition leads to ectopic fat accumulation in tissues, such as the liver and skeletal muscle, and entails an increase in cardiometabolic risk<sup>97</sup>. Ectopic fat, in humans, is thought to have a more direct role in the metabolic consequences of obesity and is considered crucial for the development of insulin resistance and lipotoxicity<sup>97</sup>. A possible role for fibrosis in adipose tissue in determining the storage capacity of peripheral adipose tissue and, subsequently, metabolic health has also been suggested<sup>98</sup>. In particular, increased SAT fibrosis assessed by collagen production but not decreased expandability assessed by measuring SAT lipogenesis (triglyceride production) was shown in humans to be associated with MAFLD<sup>98</sup>. However, these studies could not specifically determine the role of fat mass, distribution or quality in patients with lean MAFLD (n = 25) nor whether these abnormalities were a cause or a consequence of insulin resistance and the related metabolic dysfunction<sup>98</sup>.

Finally, there is likely an important genetic contribution to metabolic health<sup>1</sup>. Although no specific GWAS has been undertaken, multiple reports have identified variants, such as DCST2 rs905938 and GORAB rs10919388, that regulate body fat distribution<sup>99,100</sup>. A GWAS including up to 188,577 individuals identified 53 loci (for example, L3MBTL3, DNAH10 and CCDC92) that conferred a higher risk of cardiometabolic disease accompanied by lower levels of peripheral adiposity and higher insulin resistance (higher fasting insulin and triglyceride levels and lower HDL cholesterol) compared with healthy range<sup>97</sup>. Other studies have described favourable adiposity genes that associate with higher adiposity (subcutaneous fat) but a lower risk of liver fat, T2DM, hypertension and heart disease (including PPARG and LYPLAL1)<sup>71,101,102</sup>.

### ***The role of metabolic flexibility and adaptation for metabolic health.***

Accumulating evidence argues that metabolic health is maintained and defended via a homeostatic system<sup>103,104</sup>. Any homeostatic system requires at least three interdependent components: a signal that senses environmental stimuli and provides information, a quantitative variable that receives a measure of that signal to maintain or defend, and systems that can return the variable to its 'equilibrium' when perturbed<sup>105</sup>.

In this context, the so-called metabolic flexibility denotes the capacity of a system (cell, tissue or organism) to respond or adapt to fluctuations in metabolic or energy demands as well as the prevailing conditions or activity by rapidly and efficiently elaborating dynamic responses in the cellular machinery to adapt to the perturbation<sup>106</sup>; a progressive loss of this adaptive capacity is called metabolic

inflexibility. In the context of metabolism, this inflexibility can lead to aberrant mobilization and utilization of fat and glucose, leading to increased circulating free fatty acid concentrations and hyperglycaemia as occurs in the case of insulin resistance with hepatic fat accumulation and metabolic health-related comorbidities<sup>106</sup>.

By contrast, metabolic adaptation is defined as an alteration in the levels of organelle function to adapt to the metabolic needs of a cell or tissue (for example, in response to cold exposure or exercise)<sup>107</sup>. These adaptations involve a dynamic reprogramming of cellular metabolism, which aims to sustain cellular homeostasis and tissue viability. In this context, 'maladaptation' would denote a failure to optimally adjust to a changing equilibrium between energy demands and availability<sup>107</sup>.

Impaired metabolic flexibility or maladaptation is associated with ectopic lipid deposition in the liver<sup>108,109</sup>, insulin resistance<sup>110,111</sup>, weight gain<sup>112</sup>, MAFLD<sup>113</sup> and T2DM<sup>111</sup>. In the context of patients with lean MAFLD, the hepatic fat accumulation that results from metabolic inflexibility can occur even independently of weight gain. Metabolic inflexibility contributes to dysregulated lipid and glucose metabolism resulting in insulin resistance and dyslipidaemia, which, in turn, might contribute to systemic mitochondrial dysfunction and lipotoxicity as well as MAFLD development and progression<sup>109</sup>.

Although the notion of metabolic flexibility applies to a broad spectrum of physiological conditions, features of systemic metabolic inflexibility in patients with lean MAFLD remain elusive. As suggested in one report and depicted in Fig. 4, elevated dietary cholesterol in the context of reduced metabolic flexibility in patients with lean MAFLD (n = 538), compared with individuals who were metabolically healthy (n = 30), was associated initially with an adaptive response with increased concentration levels of bile acids in the serum, especially secondary bile acids, and increased farnesoid X receptor (FXR) activity<sup>11</sup>. These changes might maintain body weight and serum cholesterol levels<sup>11</sup>. The metabolic adaptation, as featured by elevated FXR activity and indicated by FGF19 serum levels and attenuated 7 $\alpha$ -hydroxy-4-cholesten-3-one (C4) levels (a bile acid precursor marker), might provide a plausible explanation for the consistently observed favourable histological profile in these patients, at least in the early stages of the disease<sup>11</sup>. If this hypothesis is replicated in other studies, it will imply that an individual with overweight or obesity and with MAFLD develops metabolic inflexibility earlier in the disease course than a patient with lean MAFLD. Such a scenario might have two consequences: as metabolic flexibility and adaptive responses deteriorate over time (that is, with ageing), the disease progresses, and it perhaps progresses more rapidly in patients with obesity as they would have reduced metabolic flexibility earlier. This could be one explanation for the better clinical profile of patients with lean MAFLD in cross-sectional studies<sup>11</sup> with at least equal or perhaps worse long-term adverse outcomes (Fig. 2). On the whole, it can be argued that features of metabolic flexibility are preserved across ascending orders of biological system organization in a fractal-like fashion.

From this standpoint, the transition from healthy to lean MAFLD and then to MAFLD with obesity is a manifestation of the progressive development of metabolic inflexibility. From a therapeutic perspective, it should be noted that lifestyle changes, such as exercise, in combination with healthier eating habits can improve metabolic flexibility, caloric restriction and weight loss<sup>114,115</sup>. One study of 14 adults with moderate obesity (BMI 34.0  $\pm$  1.1 kg/m<sup>2</sup>) reported a positive effect on metabolic flexibility when replacing refined-grain with whole-grain products for 8 weeks with a comparable macronutrient intake in both intervention groups<sup>116</sup>. Post-prandial glucose tolerance, peripheral insulin sensitivity and metabolic flexibility (insulin-stimulated – fasting carbohydrate oxidation) improvements were greater after whole-grain than the refined-grain diet (P < 0.05).

### ***Weight gain resistance.***

A seeming paradox in the fatty liver field is the disconnect between exposure to a strong obesogenic environment and the propensity for weight gain<sup>13</sup>. Why is it that only a subset of the population is prone to weight gain, whereas a considerable proportion remains at a normal weight? The paradox of the discovery of weight gain resistance during a period in which average adiposity in society is rising points to the existence of homeostatic systems, not yet fully discovered, for weight regulation and metabolic adaptive defence mechanisms. In contrast to traditional assumptions linking obesity and MAFLD to unhealthy lifestyle choices and a belief in the pre-eminence of self-control and willpower on these choices, accumulating evidence from human and mouse studies indicates that the propensity to weight gain and its corollary, weight gain resistance, have deep biological roots<sup>117</sup>. Characterizing these mechanisms is required to improve our understanding of obesity and its related consequences. Such an in-depth understanding might also help to minimize the stigmatization associated with obesity as a self-inflicted disease and the complexity of the factors governing dietary choices<sup>118,119</sup>. For example, following exposure to a high-fat diet, cytochrome P450 family 8 subfamily B member 1 (Cyp8b1)<sup>-/-</sup> mice were more resistant to weight gain hepatic steatosis and glucose intolerance than wild-type mice. This resistance was attributed to the fact that Cyp8b1<sup>-/-</sup> mice were characterized by increased bile acid synthesis and a greater synthesis of muricholic bile acids<sup>120</sup>. Additionally, gut microbiota was implicated in host energy metabolism and adiposity and contributed to the susceptibility of the host to high-fat diet-induced obesity by influencing several molecular processes such as lipid metabolism, circadian rhythm and homeostasis<sup>121</sup>. In this regard, germ-free rats and mice had increased bile acid synthesis and an enlarged bile acid pool and were resistant to diet-induced weight gain<sup>122</sup>. A study demonstrated that patients with lean MAFLD had increased bile acids and FXR activity compared with patients with MAFLD and obesity, implying that they were perhaps relatively resistant to obesity<sup>11</sup>. However, the mechanisms behind this varied response to diet-induced obesity remain unclear. Although these observations support the idea that bile acids counteract weight gain, it is important to emphasize that additional factors might be at play. For example, a study in Ucp1<sup>-/-</sup> mice suggested that endogenous fibroblast growth factor 21 (FGF21) acted as a master and single regulator mediating the known resistance to obesity in the absence of thermogenic adipose-specific mitochondrial uncoupling protein 1 (ref.<sup>123</sup>). Hepatic FGF21 levels were higher in patients with MAFLD than in healthy individuals, a finding that implies the existence of FGF21 resistance<sup>124</sup>.

A report demonstrated that this resistance occurred via mistranslation of FGF21 protein, which was partially inherited (FGF21 rs838133 variant)<sup>124</sup>. The role of FGF21 in patients with lean MAFLD is unknown. Another aspect not extensively researched is that, although many genes and/or loci confer susceptibility to obesity, little is known about the genetic architecture mediating healthy thinness (BMI ≤19). The latter is equally considered a distinct trait, at least as stable and heritable as obesity<sup>125,126</sup>. Few studies have sought to uncover the genetic underpinnings of thinness<sup>125,126</sup>.

A study identified anaplastic lymphoma kinase as a candidate weight-gain resistance and thinness gene in humans and mice<sup>127</sup>. The role of these variants in patients with lean MAFLD is yet to be characterized. Additionally, yet to be explored among patients with lean MAFLD is genetic susceptibility using polygenic scores that represent an individual's overall genetic susceptibility to disease. Early adult weight gain and lifetime body shape trajectory have been independently associated with excess risk of developing MAFLD in midlife. For example, a study showed that weight

gain as an adult of more or equal to 10 kg in Japanese individuals of normal weight (n = 3,503, 45.3% men) was significantly associated with MAFLD (odds ratio 1.81; P = 0.003)<sup>128</sup>. Another study of 110,054 women showed that, compared with women who maintained stable weight (plus or minus 2 kg), women with more or equal to 20 kg of adulthood weight gain had a multivariable-adjusted hazard ratio of 6.96 for MAFLD<sup>129</sup>. This observation also raised the important question of whether the progression of patients with lean MAFLD is mostly linked to overweight and/or obesity or not. In a 2021 report of health check-up data from 30,708 Korean participants who had undergone serial examinations between 2010 and 2014, independent of baseline obesity status, high weight variability (defined as the sum of absolute weight changes between successive years over the 5 years) was associated with an increased risk of developing MAFLD<sup>130</sup>. In another study, the vast majority (77.5%) of patients (n = 1,339) with lean MAFLD remained at normal weight (mean BMI 23.3 kg/m<sup>2</sup> at baseline and 23.7 kg/m<sup>2</sup> at the end of a median follow-up of 94 months) and the frequency of long-term events did not differ markedly when analysed according to change in BMI category<sup>13</sup>. Similarly, no differences were noted in adjusted hazard ratios for hepatic and extrahepatic events and mortality<sup>13</sup>. Thus, maintaining both lean and stable weight through life might offer the greatest benefit for the prevention of MAFLD. Importantly, understanding the mechanisms underlying thinness and/or resistance to obesity and its genetic basis can reveal novel anti-obesity targets for future drug development<sup>131</sup>.

Could metabolic flexibility be a target to prevent or treat MAFLD? Metabolic flexibility could be a potential target for therapy that can be exploited for MAFLD and other metabolic diseases. For example, drugs that affect fatty acid oxidation, including peroxisome proliferator-activated receptor agonists<sup>87,132</sup>, acetyl-CoA carboxylase inhibitors<sup>133</sup>, beigeing of white adipose tissue by using mitochondrial uncouplers<sup>134</sup>, AMP-activated protein kinase (AMPK) activators (such as AICAR, methotrexate and metformin) and thyromimetics targeting thyroid hormone receptors<sup>135</sup>, showed promising results in targeting metabolic flexibility to treat metabolic disease and to increase fuel utilization<sup>136,137</sup>. For example, in a randomized, placebo-controlled, double-blind, crossover study (including 11 participants with obesity), resveratrol (3,5,4'-trihydroxystilbene), a plant-derived polyphenol, activated mitochondrial biogenesis and increased mitochondrial size and density through the AMPK–SIRT1–PGC1 $\alpha$  axis<sup>138,139</sup>. Such approaches to alter metabolic flexibility and fuel selection in the context of nutrient overload seem to be attractive therapeutic strategies for obesity and metabolic diseases; these compounds remain at an early stage of clinical development. Whether such an approach would be effective and safe without unwanted adverse effects is also not known.

### ***Other lean metabolic diseases: what can we learn?***

Although obesity is an archetypal risk factor for many metabolic diseases linked with MAFLD, most of these diseases also develop in individuals of normal weight. Leveraging the shared characteristics of individuals of normal weight across these other metabolic diseases to those of patients with lean MAFLD can enhance our understanding of pathogenesis. For example, whereas most patients with T2DM also have obesity or overweight, the percentage of patients with T2DM and of normal weight ranges from 7.5% to 21%<sup>140,141</sup>. Patients with T2DM and of normal weight have fewer cardiovascular comorbidities than patients with obesity and T2DM; however, a higher frequency of insulin use indicates more rapid beta-cell failure and, therefore, an increased risk of hypoglycaemia and higher total and non-cardiovascular mortality than patients with obesity and T2DM<sup>136,142,143</sup>. Similarly, patients with hypertension and of normal weight seem to have higher mortality than those who were not of normal weight<sup>144</sup>, which is analogous to the earlier discussion on adaptive

capacity. In this regard, a systematic review and meta-analysis of 39 studies including 66,598 individuals showed that adiposity had a greater effect on hypertension in lean individuals than in those with obesity<sup>145</sup>. Collectively, it seems that, across the spectrum of metabolic diseases, patients of normal weight tend to have an increased propensity to worse outcomes compared with counterparts with overweight or obesity. Though the biological basis for this clinical observation with its pathophysiological underpinnings is elusive, it can be postulated that they share common biological roots.

### **Management of patients with lean MAFLD**

Currently, there are no specific guidelines for the management of patients with lean MAFLD, which is likely a result of the paucity of evidence available. Some studies also suggest that the discriminative performance of commonly used non-invasive scores of fibrosis, such as the NAFLD Fibrosis Score and Fibrosis-4, for clinical decision-making are suboptimal in patients with lean MAFLD<sup>146</sup>.

Some observational data showed that weight loss might be as useful in patients with lean MAFLD as in those with obesity and with MAFLD, though the required target for weight loss might be lower<sup>147</sup>. A longitudinal study of 16,738 adults with MAFLD (n = 2,383 individuals with lean MAFLD) who underwent repeated health check-up examinations showed a dose-dependent association between weight reduction and fatty liver resolution both in individuals of normal weight and MAFLD and in those with overweight or obesity and MAFLD compared with patients that showed increased weight or no weight reduction<sup>148</sup>.

Likewise, a study of 35 patients with MAFLD (n = 14 of normal weight and n = 21 with obesity) from Turkey showed that a 5% body weight loss was effective in both groups, resulting in a similar incidence of MAFLD remission<sup>147</sup>. By 6 years of follow-up, patients of normal weight with MAFLD (n = 78, baseline BMI <25 kg/m<sup>2</sup>) in a study from Hong Kong were more likely to sustain weight reduction and ALT serum level normalization<sup>149</sup>.

According to the Asian Pacific Association for the Study of the Liver guidelines, a 3–5% weight reduction might be sufficient in patients with lean MAFLD<sup>12</sup>. Poor diet quality is one of the major modifiable risk factors contributing to the deterioration of metabolic health, independent of BMI and waist-to-hip ratio<sup>150</sup>. Thus, professional dietary advice should be offered to all patients with MAFLD and to patients who are metabolically unhealthy, irrespective of their BMI status. Similarly, whereas not specific to patients with lean MAFLD, physical activity (and reduced sedentary behaviour) should be encouraged to improve metabolic flexibility and cardiovascular health. In addition to these lifestyle approaches, there should be a focus on early diagnosis and correction of the accompanying metabolic comorbidities as most patients with lean MAFLD will still die of cardiovascular rather than liver-related causes<sup>151</sup>.

### **Conclusions**

How do we move forward? Progress will only come if we tackle the problems at a societal and individual level. Despite their increased morbidity and mortality, individuals with lean MAFLD might be misclassified as healthy and overlooked by health professionals and are under-represented in clinical trials relative to the prevalence of the disease<sup>152,153</sup>. Better patient engagement in all aspects of research and implementation of MAFLD prevention and care will help adherence to clinical advice<sup>154</sup>. Increasing awareness, at a societal level, of the consequences of metabolic ill-health and integrating public health measures for MAFLD in the policies for non-communicable diseases is also critical<sup>154,155</sup>. A greater understanding of the genetic and environmental factors determining why people respond differently to the whole gamut of care is required. In the era of precision medicine, patient risk stratification into groups encompassing easily measurable and reproducible risk factors and genetic predispositions will

optimize the efficacy and cost-effectiveness of clinical care, including diagnosis and targeted lifestyle and pharmacological interventions. It is clear that, compared with MAFLD, which develops in the context of overweight and obesity, there are many unknowns in our understanding of disease development in individuals of normal weight. Answers to these questions will form the basis for developing and mapping effective preventive and therapeutic approaches for MAFLD in persons of normal weight and perhaps for individuals of normal weight and with other metabolic comorbidities. Some of the most important questions to be investigated are presented in Box 2. Initiatives bringing together diverse stakeholders across the metabolic disease spectrum are pivotal in our efforts to understand and then provide personalized, timely, equitable and affordable health interventions for patients with lean MAFLD.

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## Key points

- Lean metabolic (dysfunction)-associated fatty liver disease (MAFLD) is common, and these patients have a worse long-term outcome than patients without MAFLD.
- MAFLD in patients of normal weight likely has a similar prognosis to that in patients with overweight or obesity.
- Metabolic health is a major determinant of MAFLD pathogenesis in patients of normal weight.
- Metabolic flexibility and adaptation have major roles in shaping the metabolic health of an individual and consequently the risk of MAFLD.
- There are no specific guidelines for the management of patients of normal weight with MAFLD but lifestyle interventions remain a cornerstone of treatment.

## Box 1 | pathophysiological concepts in individuals with lean MaFID

- Metabolic health is a major determinant of metabolic (dysfunction)-associated fatty liver disease (MAFLD) pathogenesis in patients of normal weight.
- Metabolic flexibility and adaptation have major roles in shaping metabolic health.
- Genetics, epigenetics, alcohol intake, lifestyle factors such as diet quantity and quality, physical activity, the enterohepatic circulation and gut microbiota interact in a complex and dynamic manner to shape an individual's metabolic health status and consequently their risk of MAFLD.
- Homeostatic systems for weight regulation and metabolic adaptation are yet to be fully characterized but are likely implicated in weight gain resistance.
- Metabolic flexibility is likely a target for drug therapy.
- Comparing the shared characteristics of individuals of normal weight with other metabolic diseases to those of patients with lean MAFLD will be informative for understanding pathogenesis.

## Box 2 | open research questions

General questions relevant to metabolic (dysfunction)-associated fatty liver disease (MaFID) in patients of normal weight

- In what ways do environmental and external forces shape or modify our homeostatic levers?
- What are the physiological and cellular components that govern metabolic adaptation?
- How is the homeostatic 'set point' of adiposity set? Is it modified by external factors and time?
- What are the genetic and epigenetic components of the weight regulatory system?

MaFID specific questions

- Although metabolic inflexibility during exercise was reported<sup>156</sup>, is there a differential pattern of metabolic flexibility and myocellular responses during exercise between patients with lean and non-lean MAFLD, or between patients who respond and those who do not respond to lifestyle intervention?
- What variables govern metabolic adaptation specifically in patients of normal weight with MAFLD?