Anyone trying to understand the burden of disease of NAFLD in our societies might feel like they are trapped in a labyrinth, under a dim light. A labyrinth, because there are many ways to look for NAFLD and not just one straightforward diagnostic method. Under a dim light, because all these imperfect procedures and tests do not allow us to see far enough, given their limited sensitivity and specificity. Yet, for all these uncertainties, the sense of facing a real problem is overwhelmingly present. Just as it should be when you are trapped in a labyrinth.

Because of the absence of a simple and readily available marker of NAFLD, data from the general population has been slow to emerge. The report from Armstrong et al. in this issue of the Journal of Hepatology is therefore an important addition to the literature. The authors studied NAFLD in the setting of a large, primary care practice in the UK. This is a step closer to the general population although not yet as close as screening for NAFLD in factory workers [1] or through City Hall records [2]. The overall design was to identify individuals with increased liver function tests, but without a past history of liver disease, known alcohol-related health problems, past or present intravenous drug use or current symptoms of liver disease. Increased LFTs were therefore diagnosed in asymptomatic individuals with a low risk of liver disease. But this does not mean that those individuals were otherwise healthy. Most of them had chronic health problems which actually prompted testing for LFTs. In fact 40% of participating individuals were obese, 43% had arterial hypertension, and 24% had type 2 diabetes (Table 2), all conditions epidemiologically associated with NAFLD. While this is far from the end-of-spectrum seen in tertiary referral centers, it still concerns a population enriched with risk factors for NAFLD, albeit less so than reports from specialized academic centers. With these entry criteria, 1118 individuals were included. The strength of the study is that almost all of them underwent a thorough work-up including ultrasound and specialized hepatological tests, to diagnose the underlying liver disease.

The results come as a surprise to anyone that first learned what causes liver disease, a bare 20 years ago. In today's clinical landscape, 26% of these cases are related to NAFLD, 25% to alcohol consumption, and 45% have no clear cause, while all classical causes of liver diseases (HCV and HBV infection, hemochromatosis, primary biliary cirrhosis, alpha1 anti-trypsin deficiency, etc.) account for less than 1% each! Thus, NAFLD is nowadays the main player in hepatology and probably here to stay. Worse, considering how the diagnosis was ascertained, there is a fair chance that the prevalence of NAFLD might have been underestimated by a good margin. Ultrasound is notoriously unable to diagnose excess fat in the liver when this is less than 20–30% on liver biopsy. Thresholds for alcohol were conservative at best (more than 20 g/day for females and 30 g/day for males); this is in line with expert recommendations [3] but totally misses the epidemiological reality of a large segment of the population which is exposed to both metabolic risk factors and moderate amounts of alcohol (<50 g/day). Studies in the French general population have shown that almost two-thirds of patients attending a routine examination in Social Security Health Care centers have metabolic risk factors but also consume alcohol higher than 10 g/day for females and 20 g/day for males [4]. Because of their exposure to metabolic risk factors, there is no reason why these individuals should not be considered as having NAFLD (with or without alcoholic liver disease) until proven otherwise. In some large epidemiological studies, only daily amounts >30 g/day were associated with steatosis [5]. Note that in the study by Armstrong et al., 87% of the subjects with alcoholic liver disease (diagnosed with the liberal thresholds mentioned above) also happened to be overweight. On the other hand, more than half of these patients with “excessive” alcohol consumption did not have steatosis detectable by ultrasound. Despite the insufficient sensitivity/specificity of ultrasound, this questions whether the thresholds for the diagnosis of alcoholic liver disease might have been too low. Unsurprisingly, older studies establishing associations between alcohol intake and risk of alcoholic liver disease did not adjust for BMI, diabetes, or other metabolic risk factors. The lines are thus blurred until comprehensive studies of the association between exposure to metabolic risk factors and moderate alcohol consumption vs. hard outcomes become available. Meanwhile, it is reasonable to assume that the prevalence of NAFLD in asymptomatic patients with altered LFTs and no suspicion of other causes of chronic liver disease is even higher than that presented by Armstrong et al.

To their credit, Armstrong et al. avoided to some extent the usual limitations of this type of study. The vast majority of blood samples (1029/1118) were assayed in a central lab and the results of the others were standardized to the central lab refer-
ence range. The upper limit of normal was close to 40 IU/L, higher than ideal but still acceptable and in line with that used by most labs. Ultrasound was performed by senior radiologists with good inter-observer reproducibility. Nonetheless, the study was based on a single time-point instead of persistently elevated LFTs. Many subjects with increases in aminotransferases could have normal values upon retesting. This could be accounted for by transient infectious episodes, drug intake, or other circumstantial events. The proportion of cases with an unknown cause of altered LFTs could have been lower, and that of cases due to NAFLD or alcohol consumption higher than what was ultimately found by Armstrong et al. Interestingly, an increased level of serum gamma glutamyl transpeptidase appeared to have higher sensitivity than increased aminotransferases, the usual test for screening patients at risk for NASH.

These high epidemiological numbers are backed up by a few other converging reports. Earlier this year in a study performed in middle-aged, US Army personnel seeking medical care for unspecified medical conditions (but unrelated to NAFLD), the prevalence of ultrasonographically defined and histologically confirmed fatty liver was an intriguing 48% [6]. This is double the previous estimates from Western countries based on similar ultrasound detection. It may be explained by particulars of the population under study (mean BMI of 30 kg/m² and a 45% prevalence of obesity) but, remarkably and contrary to the report by Armstrong et al., patients were included irrespective of abnormal LFT values. Even more concerning are data of incidental findings of NAFLD and NASH in candidates for living-donor liver transplantation. Because of the selection process, these individuals are at lowest risk for liver disease. Yet, histological verification shows that the prevalence of steatosis alone ranges from 12–51% and that of steatohepatitis from 2% to 15% [7–12]. It should come as no surprise that the initial reports in the 90’s [13] were largely confirmed a decade later: nowadays NAFLD has become the most frequent cause of newly diagnosed cases of chronic liver disease [14].

While this study shows that NAFLD is exceedingly common in today’s practice, it is also a reminder that all patients with increased LFTs and no alcohol consumption do not, necessarily, have NAFLD. In this series, 45% of patients with a single-time increase in LFTs did not have an identifiable chronic liver disease, including NAFLD. In another series of patients with persistently elevated aminotransferases and no identifiable cause of liver disease, including alcohol consumption, only 55% had histologically documented NAFLD [15]. Twenty percent had normal or near normal liver biopsy and 25% had miscellaneous pathological conditions that did not qualify for NAFLD. Population-based surveys such as NHANES III asserting de facto that any patient with an unexplained increase in ALT has NAFLD, thus most likely have some significant margin of error.

Granted that now everyone accepts NAFLD as the front-runner in the epidemiology contest, the next question is: to what extent does it induce significant liver damage? Most available series, instead of serum markers: 2.7% of the total population and 7% those with increased LFTs, nor did they study NAFLD patients with normal LFTs. However, with a rather conservative estimate of 25% of the adult Western population having NAFLD, and only half of them with increased LFTs, between 1% and 2% of the general population might have advanced fibrosis due to NAFLD. These figures are supported by the findings of Williams et al. [6] (admittedly in a population with a high level of obesity), which used histology instead of serum markers: 2.7% of the total population and 7% of those with NAFLD had advanced fibrosis.

Of course, these estimates will be magnified in populations biased by referral patterns to specialist care. Large studies of selected NAFLD patients have shown a prevalence of advanced fibrosis (F3, F4 Kleiner) ranging between 17% and 27% and cirrhosis between 8% and 14% [18–21]. But perhaps the closest study to the one of Armstrong et al. is the French multicentric study, mentioned above [15], in which patients with unexplained increases in LFTs underwent liver biopsy. Nine out of 263 patients were found to have cirrhosis; all nine had NASH as the underlying histological diagnosis. Seventeen were found to have advanced bridging fibrosis (F3 METAVIR); all but one had NASH.

How then one can disagree with these findings of increased prevalence and fibrotic severity in patients with NAFLD and their overall impact? Simply by stating that while cirrhosis is linked to hepatic steatosis, Williams et al. showed that 30% of patients with NAFLD (at least 12% of the entire adult population that was screened) had NASH [6]. This is much higher than the conventional estimate drawn from studies performed in the 80’s and early 90’s, that showed that only 10% of patients with fatty liver have steatohepatitis. A few other recent studies with liver histology are rather in the high range found by Williams et al.: 43–55% in patients with increased aminotransferases [15,16], and as high as 49% in morbidly obese patients [17]. Considering that steatohepatitis is the main histological factor driving fibrosis progression, this means that at least one-third of patients with NAFLD are at risk of progressive disease. How many of these patients will actually develop advanced fibrosis depends on contingent factors, not all related to NAFLD: length of follow-up, inter-individual variability for susceptibility to fibrosis and competing risks from co-morbid associations. But the point here is that, even in unselected populations, a significant proportion of patients with NAFLD are at risk of disease progression and thus should be monitored and treated accordingly.
increased liver-related mortality, bridging fibrosis will not kill anyone; therefore, the high numbers of NAFLD patients with bridging fibrosis will in fact not experience liver-related morbidity or mortality. While this makes sense today, tomorrow might be different. Liver fibrosis does progress, although, admittedly, at a different pace in different individuals. Patients with bridging fibrosis have reached this stage because of active fibrogenesis; this will not stop once the diagnosis has been made, provided that the underlying disease is still present (in fact it might even be that with increasing age, fibrosis will progress faster). There are long-term prognostic data that support this contention, as they show an increase in liver-related mortality or complications of cirrhosis even in patients with bridging fibrosis but without cirrhosis. For instance, patients with NAFLD and bridging fibrosis had an independent 5.7-fold increase in liver-related mortality over those without bridging fibrosis [22]. In chronic hepatitis C, the HALT-C trial demonstrated an association between fibrosis stages and liver-related clinical outcomes [23], already starting at the advanced bridging fibrosis stage. In a Japanese long-term follow-up study, patients with early bridging fibrosis (F2 META-VIR) had an independent 8-fold increased risk of liver-related death over those with no or mild fibrosis (F0, F1 META-VIR) [24]. That clearly shows that in the mid-term, bridging fibrosis is not benign. Granted, the individual predisposition to fibrosis might be different between NAFLD and HCV, in the sense that a lesser proportion of patients with NAFLD than with HCV have advanced fibrosis. However, for those who already have bridging fibrosis, the prognosis should be the same. Micromorphometry studies have indeed shown that for a given histological stage and after adjustment for all main cofactors of fibrosis, patients with NAFLD have the same amount of fibrosis than those with HCV [25].

NAFLD is increasingly frequent in the general population, and the number of those at risk of disease progression and of those having advanced disease is clearly a concern. The next chapter is to determine what is best to do about it, as far as screening efforts, therapy and cost effectiveness. Fortunately, we are taking on this new task based on a firm ground provided by these epidemiological studies. So much the better that the labyrinth is not built on moving sands…

Conflict of interest

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References


