The epidemiology of fatty liver

Stefano Bellentani[a], Giorgio Bedogni[a], Lucia Miglioli[a] and Claudio Tiribelli[b]

There are insufficient data available on the epidemiology of fatty liver to design a complete and correct view of the prevalence, incidence and natural history of this disorder. This article, mainly based on the revision of recently published papers in this field, attempts to give an overview of the current findings on the epidemiology of fatty liver worldwide. The possible factors involved in the development of fat accumulation in the liver, and their potential role in the progression of the disorder will be also addressed. ***Eur J Gastroenterol Hepatol*** **16:1087–1093 © 2004 Lippincott Williams & Wilkins**

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[a]Fondo Studio Malattie del Fegato-ONLUS, Trieste and Modena, Italy. [b]Centro Studi Fegato, Building Q, AREA Science Park, Basovizza, and Department BBCM, University of Trieste, Trieste, Italy.

Correspondence to Dr Stefano Bellentani, Fondo Studi Fegato – Sezione di Campogalliano (MO), Via R. Luxemburg, 29/N, 41011 Campogalliano, Modena, Italy.
Tel: +39 059 371102; fax: +39 059 851762; e-mail: liversb@unimore.it

Introduction

Hepatic steatosis or fatty liver is an infiltration of fat, mainly triglycerides, inside hepatocytes, usually exceeding 5% of the liver weight [1]. Traditionally, fatty liver has been considered a benign and reversible condition, usually the expression of a non-specific response of the liver to metabolic stress of different origin [2,3]. In routine clinical practice, fatty liver is usually associated with an alteration of either alanine aminotransferase (ALT) or gamma glutamyl transferase, and most cases, especially in the past, have been usually linked to undeclared alcohol abuse. In addition to alcohol abuse, other aetiological factors for fatty liver are obesity, diabetes and hypertriglyceridaemia (all components of the so-called 'metabolic syndrome') [1], but the relative role of each of these factors in fatty liver is still undefined.

Although non-invasive diagnostic procedures, such as ultrasonography or computed tomography, have become sufficiently sensitive to diagnose fatty liver, in clinical practice it is still impossible to distinguish between simple steatosis and steatohepatitis without performing a liver biopsy. However, it is often difficult and sometimes unethical to propose a liver biopsy to a subject who is apparently healthy, in particular in view of the lack of an effective therapy. However, in the light of new knowledge, fatty liver, especially macrosteatosis, when associated with liver necrosis or inflammation, due either to alcohol abuse (alcoholic steatohepatitis (ASH)) or to other causes, mainly metabolic (non-alcoholic steatohepatitis (NASH)) is increasingly recognized as a condition that could evolve into fibrosis, cirrhosis and, possibly, hepatocellular carcinoma [4–6]. Fibrosis leading to cirrhosis can accompany virtually any chronic liver disease that is characterized histologically by the presence of hepatobiliary distortion and/or inflammation [7]. The majority of studies available on the epidemiology of fatty liver have been performed in selected series and with retrospective designs, and not on the general population. During the last 5 years, after a consensus agreement on the definition of NASH and non-alcoholic fatty liver (NAFL), and after the discovery that NAFL and NASH are one of the most frequent causes of alteration of liver enzymes, and of cryptogenic cirrhosis [4], a very large number of research papers have been published, and data collected on the general population have become available [8,9].

In this review we try to determine the prevalence, natural history and major risk factors for fatty liver by considering the most recent data available in the literature. Particular attention is paid to data collected from the general population.

Definitions of non-alcoholic and alcoholic fatty liver disease, and non-alcoholic and alcoholic steatohepatitis

Non-alcoholic fatty liver (NAFL) and alcoholic fatty liver (AFL) are conditions characterized by a significant accumulation of lipids inside the hepatocytes, the former without a history of excessive alcohol consumption, the latter linked to alcohol abuse [4]. NAFL and AFL encompass a wide spectrum of liver injury, ranging from steatosis to steatohepatitis, fibrosis and cirrhosis [5]. Non-alcoholic steatohepatitis (NASH) is a stage of NAFL characterized by histological lesions similar to those of alcoholic steatohepatitis (ASH) [5]. The term was coined in 1980 by Ludwig *et al.* [10] to describe the morphological pattern of liver injury in 20 patients evaluated at the Mayo Clinic over a 10 year period. These patients had histological evidence of alcoholic hepatitis on liver biopsy without a history of

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alcohol abuse. While simple steatosis has a benign clinical course, NASH may evolve into fibrosis, cirrhosis and, possibly, hepatocellular carcinoma [4]. Because NASH cannot be distinguished from ASH on histological grounds, its diagnosis relies heavily on the determination of the quantity of alcohol consumed by the patient [6]. However, there is lack of consensus on what represents 'excessive' alcohol consumption. Studies on NAFL published before 1990 allowed no alcohol consumption, while those published subsequently allowed up to 210 g/week, i.e., 30 g/day [6,11,12]. In the Dionysos study, a study on the prevalence of chronic liver disease in a general population of 6917 apparently healthy subjects [8,13–15], we also found that the risk threshold for the development of ethanol-induced liver disease was the ingestion of more than 30 g of alcohol per day. However, only 74 out of 1349 individuals at risk (5.5%) actually showed persistent signs of alcoholic liver damage [13]. In spite of the axiom 'no alcohol, no damage', the epidemiological data correlating alcohol consumption and risk of alcoholic liver disease suggest that alcohol consumption might not be the only determinant of this group of diseases. Although the hepatotoxicity of ethanol has been well established, clinical experience suggests a wide individual susceptibility to alcoholic liver disease in a given population, and data available confirm that only a proportion ranging from 5% to 30% of chronic alcoholics develop cirrhosis [11–15]. Thus, one is forced to postulate that the relation between alcohol consumption and cirrhosis is a multifunctional phenomenon that also involves the interplay of other factors, such as drinking habits, pattern of drinking, gender and genetic factors [16–22]. Hepatic steatosis can be induced, however, by drinking 20 g of alcohol per day [23] and this is the upper limit now generally accepted and employed by recent studies on NAFL [6]. This is the limit we will use in this review to separate NAFL from AFL, and NASH from ASH.

Prevalence of fatty liver, NAFL and NASH

Although the role of alcohol consumption and obesity in inducing fatty liver has been reported, their joint role is still undefined, and the prevalence, incidence and natural history of fatty liver in the general population has long been controversial. The majority of the available data belongs either to retrospective studies on mortality, or to hospitalized patients and provides only a piece of the whole puzzle. Previous studies [4,6] reported a prevalence of steatosis ranging from 1% to 51% – this large variability possibly explained by the different types of populations studied, and by different ways in considering the role of more than one factor inducing steatosis. Apart from the Dionysos study [8,9,13–15], a complete analysis of the prevalence of fatty liver, including the various risk factors, does not exist. In contrast, the epidemiology of NAFL has been correctly determined, especially during the last 5 years. NAFL is an increasingly common problem worldwide [24] and its prevalence is estimated according to both the type of population investigated and the methodology used (clinical series, imaging or autopsy studies, and general population screening) [24–39]. As shown in Table 1, by using different methodologies and by considering different countries, results are quite different. In selected series of patients undergoing liver biopsy, the prevalence of NAFL ranges between 15% and 51% [26,28–33,36]. This wide range is certainly due to different study designs and different criteria in recruiting the patients. For example, in the study by Propst *et al.* [31] where the prevalence of fatty liver was 15% (Table 1), the screening criterion was the presence of fatty liver at ultrasound, while in the study by Hultcranz *et al.*

Table 1 Prevalence of non-alcoholic fatty liver (NAFL) and non-alcholic steatohepatitis (NASH) in different countries, according to different study populations

Study population, methods of screening, and first author	Country	Number of subjects	Prevalence of NAFL (%)	Prevalence of NASH (%)
Autopsy random series, liver biopsy, Hilden [25]	Sweden	503	24	ND
Hospital series, liver biopsy, Hultcrantz [26]	Sweden	149	39	ND
Outpatient series, ultrasound, Lonardo [27]	Italy	363	20	ND
Hospital series, liver biopsy, Berasain [28]	Spain	1075	ND	16
Population study, ultrasound, Bellentani [9]	Italy	257	16	ND
Autopsy random series, liver biopsy, Ground [29]	USA	423	16	ND
Hospital series, liver biopsy, Lee [30]	USA	543	ND	9
Hospital series, liver biopsy, Propst [31]	USA	35	15	5
Hospital series, liver biopsy, Byron [32]	USA	1226	ND	11
Hospital series, liver biopsy, Daniel [33]	USA	81*	51	32
Autopsy series, liver biopsy, Wanless [34]	Canada	207**	29	6
Population study, ultrasound, Nomura [35]	Japan	2574	14	ND
Hospital series, liver biopsy, Nonomura [36]	Japan	561	ND	1
Outpatient series, ultrasound, Omagari [37]	Japan	3432	9***	ND
Outpatient series, ultrasound, Araujo [38]	Brazil	217†	33.5	ND
Outpatient series, ultrasound and CT scan, El-Hassan [39]	Saudi Arabia	1425	10	ND

*Subjects with NAFL and AFL, therefore the prevalence is relative to fatty liver. **Obese subjects. ***The authors report a prevalence of fatty liver of 21.8%. †Female obese subjects. ND, not determined.

(prevalence of fatty liver = 39%, see Table 1) [26], biopsies were performed in all the patients with persistent elevation of transaminases. The highest prevalence of both NAFL (51%) and NASH (32%) has been found by Daniel *et al.* [33] in the USA, but their series included all patients with both NAFL and AFL, reflecting probably the real prevalence of fatty liver in selected hospitalized patients undergoing liver biopsy. It must be stressed that, since patients undergoing liver biopsy are specifically selected, these data do not reflect the real prevalence of fatty liver and NAFL in the general population. More accurate estimates can be obtained either from studies investigating subjects who had casual deaths, such as autopsies performed on individuals who died randomly from automobile [25] or aircraft accidents [29], or from studies performed on general populations or outpatient screening [9,27,35,37–39]. Between the two studies performed in subjects who randomly died in automobile or aircraft accidents, probably the most accurate estimate of the prevalence of NAFL is 16%, as derived from the study by Ground [29], since it included only crew members, where significant alcohol use could be reasonably excluded (Table 1). Finally, in studies performed in non-obese subjects, either in an outpatient series [27,37–39] or in general populations [9,35], where ultrasonography or computed tomography was used to make the diagnosis of fatty liver, the prevalence of NAFL is quite similar, ranging from 10% in Saudi Arabia [38] to 9–14% in Japan and 16–20% [9,27] in northern Italy (Table 1). However, these studies are not able to distinguish between NAFL, NASH and cryptogenic cirrhosis, because, usually, a liver biopsy is not performed. The best current estimates are that the prevalence of NAFL in the general population is approximately 20% and of NASH 2–3%, making these conditions the most common liver disease in the US and Western countries [40].

NASH is also becoming increasingly recognized in children, and may lead to cirrhosis during childhood [4].

Prevalence of fatty liver in the Dionysos cohort

The only published study performed in the general population which considered different causes of fatty liver is the Dionysos study [9,15]. This study was performed in a cohort of apparently healthy subjects, aged 12–65 years, resident in two towns of northern Italy, and, which now, have been followed up for 10 years. During the first screening in 1991–1992, following the criteria for classifying suspected liver disease [8] we observed an overall prevalence of steatosis of 61% (M:F ratio of 3), according to the international guidelines for the definition of fatty liver at ultrasound [41]. Fatty liver was detected in 33% of HBsAg HBV DNA positive subjects, and in 44% of the anti-HCV HCV RNA positive subjects. As shown in Table 2, following the accepted alcohol intake threshold of 20 g/day for the classification of NAFL, within the Dionysos cohort, after exclusion of HBsAg and anti-HCV positive subjects, NAFL was present in 91% of obese versus 67% of overweight people ($P < 0.0001$) and 24.5% of subjects with normal weight ($P < 0.0001$), while AFL was present in 94% of obese versus 84% of overweight people ($P < 0.0001$) and 56% of subjects with normal weight ($P < 0.0001$). These results are very similar to those recently reported in Japan by Omagari *et al.* [37] in an outpatient series of 3432 adult Japanese in the area of Nagasaki who underwent medical examinations in 2000.

An intra-cohort study, performed in 2000 by using ultrasonography, allowed an understanding of the 'real' prevalence of fatty liver and defined the subjects at risk for the hepatic fat accumulation [9]. After exclusion of HBsAg and anti-HCV positive subjects, and those who consumed any type of drug during the previous 6 months, we were able to evaluate the separate effects of alcohol consumption and overweight on the frequency of fatty liver. The overall prevalence of steatosis in this selected series was 58%. Prevalence of fatty liver at ultrasonography increased progressively and significantly from 16% in controls, non-drinkers and lean subjects, to 46% in heavy drinkers (> 60 g/day) with normal body mass index, 76% in obese subjects who were teetotallers, and 94.5% in obese subjects who drank heavily. The risk ratio for steatosis significantly increased in heavy drinkers (2.8), obese (4.6), and obese and heavy drinkers (5.8). Obesity increased the risk of steatosis two-fold in heavy drinkers while heavy drink-

Table 2 Prevalence of fatty liver in the Dionysos cohort at the first screening [8], after exclusion of HBsAg and anti-HCV positive subjects, according to body mass index (BMI) and alcohol consumption

BMI classification	NAFL (⩽ 20 g alcohol per day), *N*/total	AFL (> 20 g alcohol per day), *N*/total
Normal (⩽ 25)	34/139 (24.5%)	59/105 (56%)
Overweight (> 25 but < 30)	104/155 (67%)	179/213 (84%)
Obese (⩾ 30)	61/67 (91%)*	91/97 (94%)*
Mean	199/361 (55%)	329/415 (79%)

*$P < 0.0001$ versus overweight and normal (Pearson's chi-square 2 × 3 table). NAFL, non-alcoholic fatty liver; AFL, alcoholic fatty liver.

ing was associated with only a one-fold risk in obese subjects. Most important was the demonstration that steatosis was more strongly associated with obesity (76%) than heavy drinking (46%), suggesting a greater role of overweight than inappropriate alcohol consumption in inducing fat accumulation in the liver. According to the recently performed 'Nutrition & Liver Study', a case–control study aimed at assessing the prevalence of and the risk factors for fatty liver and NAFL in the Campogalliano cohort of the Dionysos study, the prevalence of fatty liver in the general population is 43% and that of NAFL is 21% (unpublished data).

Nowadays, there is an overall agreement to conclude that (1) the mean prevalence of fatty liver in the general population, as measured by ultrasonography, ranges from 20% to 60%, at least in Western countries; (2) it is more frequent in men than in women (3/1 ratio); (3) is less prevalent in lean and teetotaller subjects (16–24%); and (4) it is much more prevalent in alcohol abusers (46–50%) and obese people (76–89%).

Risk factors and natural history of fatty liver

The traditional causes of fatty liver are generally considered to be nutritional, metabolic, toxic and genetic factors. Summaries of the main causes that may produce fatty liver are reported in Table 3. For each cause listed there was at least one report in the literature. Among this rather long list, there are well-documented risk factors, which usually differ between fatty liver and NAFL. Male gender, the amount of alcohol, the duration of drinking, the type of alcoholic beverage and the way of drinking have been recognized as risk factors for inducing not only fatty liver, but also cirrhosis [11–14]. To define the natural history of fatty liver, however, the risk factors linked to the progression of the disease are more important. As reported above, fatty liver has been always considered a benign and reversible condition [1]. However, recently, NAFL and NASH have been recognized as inducing fibrosis and progressing to cirrhosis, although in a small percentage of subjects [42–47]. Several studies have looked at the possible predictors for the progression of NAFL and NASH to cirrhosis [3–7,24,42–47], and at the differences in natural history between NAFL and NASH. Teli *et al.* [3] suggested that subjects with steatosis and non-specific hepatic inflammation (without NASH) are less likely to progress to fibrosis and cirrhosis. In a retrospective study of 136 patients followed up for 10 years, Matteoni *et al.* [46] extensively reported the importance of relating the natural history of NAFL to the different histological forms.

Cirrhosis developed predominantly in type 3 (fat + ballooning degeneration) and type 4 (fat + fibrosis and Mallory bodies) than in type 1 (fat alone) and type 2 (fat + inflammation) NAFL. Interestingly, the early finding of Mallory's hyaline, ballooning degeneration or fibrosis was found to be predictive of a more clinically serious outcome [48]. Clinical and laboratory data, such as age >45 years, type II diabetes mellitus, and aminotransferases elevation, were found to be significant risk factors for the progression of NAFL to fibrosis [45]. On the basis of these findings, age, body mass index, serum ALT and triglyceride levels were combined in a scoring system (still awaiting validation) to predict fibrosis [49]. As in viral hepatitis, the aspartate transaminase/ALT ratio has been suggested as a predictor of fibrosis in NAFL [46], and may be helpful in ruling out an alcoholic aetiology [50]. In contrast, no positive correlation has been found between serum and

Table 3 Main causes of fatty liver

Nutritional	Metabolic or genetic	Drugs and toxins	Other
Alcohol abuse	Diabetes	Amiodarone	Toxic mushrooms
Obesity	Hyperlipidaemia	Methotrexate	Inflammatory bowel disease
Protein malnutrition	Acute fatty liver of pregnancy	Oestrogens	Small-bowel diverticulosis with bacterial overgrowth
Starvation	Lipodystrophy	Corticosteroids	Human immunodeficiency virus infection
Rapid weight loss	Dysbetalipoproteinaemia	Tamoxifen	*Bacillus cereus* toxin
Gastrointestinal surgery for obesity	Wolman's disease	Aspirin	Rapeseed oil
Total parenteral nutrition	Cholesterol ester storage	Calcium-channel blockers	Herbal medicaments
		Valproic acid	
		Thioridazine	
		Tetracycline	
		Clorphenilamine	
		Cocaine	
		Zidovudine	
		Didanosine	
		Fialuridine	
		Griseofulvin	
		Hychantone	
		Chloroquine	
		Coralgil	
		Environmental toxins (e.g., hydrocarbons, dimethylformamide, phosphorus)	

tissue iron levels and the progression of NAFL to cirrhosis [51,52]. Female gender, age >45 years, diabetes mellitus, hyperinsulinaemia, obesity and hypertriglyceridaemia are traditional risk factors for NAFL [42–44].

As reviewed by Angulo *et al.* [45], the prevalence of obesity in patients with NAFL varies between 30% and 100%, that of type 2 diabetes between 10% and 75%, and that of hyperlipidaemia between 20% and 92%. In the Dionysos study, the prevalence of NAFL was 4.6 times higher in obese than in non-obese individuals [9]. More recently, Ruhl and Everhart in a national, population-based study, where almost 6000 American adults who participated to the third NHANES survey were recruited [53], clearly demonstrated that obesity, particularly central adiposity, hyperleptinaemia and hyperinsulinaemia were the major determinants of the association of overweight with elevated serum ALT levels.

Insulin resistance is common in obesity and hypertriglyceridaemia, and is the hallmark of type 2 diabetes. It is frequently detected in patients with NAFL, with and without obesity and diabetes [54–59]. Thus, insulin resistance may be the minimum common denominator in most cases of NAFL [45,59]. Insulin resistance, impaired glucose tolerance, obesity and hyperlipidaemia are all elements of the metabolic syndrome [54] so that NAFL has been considered another 'disease of affluence' [59]. In a recent study, Marchesini *et al.* [56] assessed the prevalence of the metabolic syndrome in 304 consecutive NAFL patients without diabetes. Not surprisingly metabolic syndrome was observed in 18% of subjects with normal weight and 67% of obese subjects but, interestingly, 88% of the patients with NASH had the metabolic syndrome as compared to 53% of those with simple steatosis. Of note was the observation that the metabolic syndrome, but not iron overload, was a predictor of fibrosis, suggesting an independent pathogenetic role of this condition in the natural history of the liver disease [52,56]. Collectively, these data point to the conclusion that insulin resistance *per se* may be a risk factor for the progression of simple steatosis to NASH, even if a cause–effect relationship can be disclosed only by prospective studies. In line with this conclusion was the hypothesis that insulin may play a central role in the pathogenesis of NASH by the so-called 'two-hit' theory [60–62]. The 'first hit' consists of the development of hepatic steatosis owing to insulin resistance while the 'second hit' would be oxidative stress, mainly in the form of an excessive production of reactive oxygen species from the mitochondria of lipid-laden hepatocytes. Recent studies have shown that insulin resistance is a risk factor for NASH [56–59], therefore, insulin itself may act as a 'second hit' [60]. Contrary to cardiovascular and metabolic disease, at present there is no evidence that dietary intake is associated with either NAFL or NASH. However, Musso *et al.* [63] have recently described a higher intake of saturated fatty acids and cholesterol and a lower intake of polyunsaturated fatty acids, fibre, ascorbic acid and tocopherol in 25 patients with NASH as compared to 25 healthy controls. Although obtained in a selected sample and awaiting confirmation, these findings are of interest because they are similar to those obtained for cardiovascular and metabolic disease, at least as far as fats and fibre are concerned [51]. Further prospective and larger studies are necessary to confirm this potentially important information.

Finally, some data suggest that the co-existence of steatosis with hepatitis C virus infection could increase the risk of progression to cirrhosis [64].

Interesting data on the natural history and determinants of disease progression of NAFL and NASH were recently provided by Saksena who followed up 91 patients with histologically proven primary NAFL (62 with simple fatty liver and 29 with NASH) for 8 years. Though only published in abstract form so far [65], 11% and 10% of patients with, respectively, simple fatty liver or NASH at the first biopsy showed histological worsening and progression to either fibrosis or cirrhosis. The only two factors associated with disease progression were the severity of steatosis and the high activity promoter polymorphism of the CD14 endotoxin receptors, which is known to be associated with NASH [56]. These data suggest that a small percentage (around 10%) of both fatty liver and NASH usually progress to fibrosis and cirrhosis over a long period of time, and that this progression is probably due to genetic factors, as demonstrated for alcohol-induced liver disease and ASH [16,17,22].

Incidence of fatty liver

The calculation of the true incidence of fatty liver, i.e., the number of new cases of fatty liver in a known interval of time, implies the availability of prospective population studies. We can guess that just because the prevalence of obesity is progressively increasing in Western countries, also fatty liver, and especially NAFL and NASH, will increase in the next years. We have some preliminary information from the population who participated in the Dionysos study in 1991–1992, and that has been followed up for 10 years and re-screened again in the years 2001–2002.

Among the sub-cohort of people who underwent ultrasonography, and who participated in both the first and second screenings the balance seems to be positive: 29% resolved fatty liver in 10 years, while 20% devel-

oped fatty liver, suggesting an incidence of 2% of new fatty liver cases every year.

Conclusions

According to the data available, especially those relative to studies of the general population, we may conclude that fatty liver, especially NAFL, is now the major cause of elevation of ALT [53,65,66], and is becoming the most common cause of chronic liver disease in Western countries [67]. However, in spite of the prevalence of this disorder, and its easy recognition (particularly after the routine use of ultrasonography), the underlying mechanism for the development of these diseases is still undefined and needs additional work. We are therefore sure that unravelling the relationship between nutrition factors, metabolic syndrome, fatty liver and NASH will keep our younger hepatologists very busy in the future.

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Conflict of interest

None.

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• Of special interest
•• Of outstanding interest

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