

Review

Epidemiology of non-alcoholic fatty liver disease in China[☆]

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Fatty liver (steatosis) is highly prevalent in China and is more often linked to obesity than to alcoholism. Among more affluent regions of China, the community prevalence of non-alcoholic fatty liver disease (NAFLD) is ~15%. With the increasing pandemic of obesity, the prevalence of NAFLD has approximately doubled in the past decade. The risk factors resemble those in other ethnic populations, but it is important to note that ethnic-specific definitions of central obesity, obesity and metabolic syndrome are more useful in assessment of Chinese people. The full range of histological manifestations of NAFLD has been demonstrated in Chinese patients, but to date hepatic severity is generally mild. In contrast to chronic hepatitis C, steatosis is less common in patients with chronic hepatitis B; it is associated with metabolic, and not viral factors and does not appear to affect disease severity. Although long-term outcomes of NAFLD in Chinese populations remain unclear, it may be a predictor of metabolic disorders, diabetes and cardiovascular disease. Public health interventions are therefore indicated to halt or reverse the national trend of obesity in China so as to improve liver as well as metabolic health.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is an acquired metabolic stress-related liver disorder that was originally assumed to be largely confined to resi-

dents of affluent industrialized Western countries [1,2]. NAFLD now affects 20–30% of the general population in North America and similar countries [1,2]. However, obesity and insulin resistance, the common substrates of NAFLD, are not restricted to the West, as witnessed by their increasingly universal distribution [1,3–6]. Recently, the once “lean” Chinese are facing a weight problem that is growing rapidly [4,5]. According to the first comprehensive National Health Survey on the China mainland conducted in 2004, 60 million (4.6% of the population) are obese, 200 million (15%) overweight, 20 million (1.5%) have type 2 diabetes mellitus (T2DM), and 160 million (12%) have high blood pressure [4,5]. The steadily increasing prevalence of obesity, coupled with T2DM, dyslipidemia, hypertension and ultimately the metabolic syndrome (MetS) has put a very large proportion of the Chinese population at risk of developing NAFLD in the coming decades [3,6]. NAFLD is therefore emerging into a new significant health problem in a country [3,6], where, traditionally, clinicians have dealt with the formidable burden of chronic hepatitis B virus (HBV) infection [2,7].

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Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; CHC, chronic hepatitis C; FPG, fasting plasma glucose; HBV, hepatitis B virus; HBsAg, hepatitis B virus surface antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HOMA-IR, homoeostasis model assessment-insulin resistance; IGT, impaired glucose tolerance; MetS, metabolic syndrome; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PGC-1 α , peroxisome proliferator-activated receptor-gamma co-activator-1 α ; PPAR- γ , peroxisome proliferator-activated receptor-gamma; SNPs, single nucleotide polymorphisms; SVR, sustained viral response; T2DM, type 2 diabetes mellitus; TNF- α , tumor necrosis factor-alpha.

2. Definitions of NAFLD and metabolic syndrome in China

NAFLD encompasses a spectrum of liver disorders characterized by *macrovesicular* hepatic fat accumulation alone (simple steatosis), or accompanied by signs of hepatocyte injury, mixed inflammatory cell infiltrate, and variable hepatic fibrosis in pericellular distribution (non-alcoholic steatohepatitis, NASH); NASH may lead to cirrhosis and hepatocellular carcinoma (HCC) [1,8]. Although histological examination remains the gold standard for the diagnosis of NASH, pathological definition is often not possible in community-based research studies and clinical practice settings [1,3]. Alternatively, operational definitions of NAFLD have been proposed in which biochemical criteria and hepatic imaging (ultrasonography, computed tomography, and magnetic resonance imaging) are used [9–12]. Among them, ultrasonographic definition of steatosis has most frequently been used in Chinese epidemiological research studies [3,6,9–11], and this approach has been endorsed by Asia-Pacific regional guidelines [12].

Diagnosis of fatty liver by ultrasonography is defined by the presence of at least two of three abnormal findings: diffusely increased echogenicity ('bright') liver – with liver echogenicity greater than kidney or spleen, vascular blurring, and deep attenuation of ultrasound signal [9]. In addition, other liver diseases should be excluded [8–12]. In recent studies, the etiology of steatosis has been further defined according to the Chinese Liver Disease Association criteria of 2003 [10], which include alcoholic fatty liver disease (alcohol consumption more than 40 g *per day* for more than 5 years), NAFLD (non-drinkers, or alcohol consumption less than 40 g *per week* for the past 12 months, and life-time cumulative consumption less than 100 kg), and steatosis related to other etiologies, such as chronic hepatitis C (CHC) [10,11]. The working definition of NAFLD in China is generally consistent with the recently published 2007 Guidelines for the Assessment and Management of NAFLD in the Asia-Pacific region [10–12]. However, given the high prevalence of both MetS (~15%) and chronic HBV infection (~10%) in the general Chinese population [2,5,7], it is likely that NAFLD could co-exist with other liver diseases [13–15].

Body mass index (BMI) and waist circumference are the best predictors of NAFLD, as well as of metabolic disorders such as T2DM, dyslipidemia, and MetS [6]. However, only 2–3% of Asians would be classified as obese by Western criteria [6,16]. It is well known that there is a higher proportion of visceral fat and a lower proportion lean body mass in Asians than in Caucasians with the same BMI [17]. Therefore, regional definitions of central obesity, obesity and MetS have been used widely in Chinese studies [4–6,16]; these are summarized in Table 1.

Table 1
Revised criteria of metabolic syndrome used in Chinese studies

The metabolic syndrome is defined by any three of the following factors	
Central obesity	Waist circumference ≥ 90 cm (male), ≥ 80 cm (female)
<i>and/or</i>	<i>and or</i>
Obesity	BMI ≥ 25 kg/m ² in both sexes
Hypertriglyceridaemia	Triglycerides ≥ 1.7 mmol/L
Reduced HDL-C	LDL-C < 1.03 mmol/L (male) and < 1.29 mmol/L (female)
Raised blood pressure	Blood pressure $\geq 130/85$ mmHg
Raised fasting plasma glucose	FPG ≥ 6.1 mmol/L, or previous diagnosed type 2 diabetes

BMI, body mass index; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; FPG, fasting plasma glucose.

3. Prevalence of NAFLD in China

Globally, the *incidence* of NAFLD remains unknown because no prospective studies have been conducted [1–3,6]. Further, the point prevalence of NAFLD at each of its different stages (simple steatosis, NASH, cirrhosis) remains poorly defined throughout the world [1–3,6]. The reported point prevalence of NAFLD varies widely, mainly based on the information available in a given population and the diagnostic criteria used [1–3]. From mainland China, ultrasound surveys for fatty liver (any cause) were first published in the mid-1990s [14]. The median prevalence of ultrasonographic steatosis in Chinese populations was ~10%, but ranged from 1% to more than 30% [14,15]. The factors identified to correlate with such variability included age, gender and geographic locality (*urban higher than rural, eastern coast higher than inland*), as well as the precise criteria used for disease definition [14,15]. In addition, the prevalence of fatty liver varied by occupation, being highest in administrative officers and white collars, followed (in order) by laborers, peasants, and monks [14]. The reasons for the latter differences in terms of diet, physical activity or other factors have not yet been explored.

Recent studies indicate that prevalence of fatty liver in the general population of Shanghai (East China) and Guangdong (South China) are 17% and 15%, respectively [18,19]. In these surveys, ultrasonographically detected steatosis was more strongly associated with obesity than with heavy drinking [18,19], *although the latter remains important in some other regions of China* [20]. Further, nearly 90% of cases of fatty liver appeared attributable to metabolic factors (NAFLD), the prevalence of which was therefore established to be between 12% and 15% of the general adult population [18,19]. The point prevalence of NAFLD in children and adolescents between the age of 7 and 18 years was reported to be 1.3% in Guangdong [19]. Similar findings have been observed in epidemiological surveys from

other affluent industrialized regions of China (the results have *published in Chinese but not English*) [14,15]. In addition, the prevalence of NAFLD in Hong Kong Chinese was 16% [21], and in an adult population of Taiwan it was 12% [22].

Of particular interest, the prevalence of fatty liver in Shanghai and Wuhan (capital of Hubei province, central China) has approximately doubled in the past 7–10 years [23,24]. Specifically, it has increased from 13% to 25% in participants of routine health examinations in the Shuiguohu district of Wuhan [24], and from 4% to 14% in Shanghai BaoSteel Group employees [23]. Among the latter, the prevalence of fatty liver in participants with elevated serum alanine aminotransferase (ALT) levels (>40 U/L) increased from 26% to 51% between 1995 and 2002 [23]. There is strong evidence that the substantially increased prevalence of fatty liver in the studied population during the last decade is in parallel with regional trends in over-nutrition, obesity, T2DM, dyslipidemia, and MetS [4,5,23]. Conversely, the prevalence of habitual alcohol drinking did not change over the study period [23]. NAFLD is now becoming a major cause of asymptomatic elevation of liver enzymes among those participating in regular health examinations on the China mainland and in Taiwan [23,25]. Finally, the present upward trends in the obesity and T2DM pandemic lead us to forecast a further increase in NAFLD prevalence in the immediate future [4–6].

4. Risk factors for NAFLD in Chinese patients

A detailed analysis of the available epidemiological data shows that risk factors for NAFLD in China resemble those in the West and in other regions of Asia [6]. The major ones are central obesity, obesity, dyslipidemia, T2DM, arterial hypertension, insulin resistance, for example, as measured by the homeostasis model assessment-insulin resistance (HOMA-IR), and MetS [6,14–16,18–22,25–30]. On one hand, MetS is a strong predictor of NAFLD [6,16,29,30]. On the other hand, NAFLD is a good predictor for the clustering of components of risk factors for MetS [30]. In a recent Hong Kong study, hypoadiponectinemia was associated with NAFLD (*vs.* controls), while serum tumor necrosis factor- α (TNF- α) levels (as well as BMI) were independent factors for NASH (*vs.* simple steatosis) [31]. Other work has shown that low serum adiponectin levels correlate with steatosis severity, and with necroinflammatory severity of NAFLD (i.e., the presence of NASH versus simple steatosis) [8,32]. *In addition*, impaired glucose tolerance (IGT) without elevation of fasting plasma glucose (FPG) is common among Hong Kong Chinese patients with NAFLD and no history of T2DM [33]. In a large international study, IGT was associated with

histologically severe liver disease in NAFLD [34], but the study by Wong and colleagues indicated that histological severity could not be accurately predicted by any FPG cut-off [33].

It is often stated that there are apparent differences in risk factors for NAFLD between Chinese and Caucasians, particularly a perception that NAFLD can occur in “lean” Asians, but not Europeans [6,16]. This could be because inappropriate anthropometric criteria have been used for waist circumference and BMI in Asians [4–6,16]. Even the use of the ethnic-specific overweight and obesity criteria reveals a relatively high proportion ($\sim 40\%$) of Chinese NAFLD patients with normal BMI [22,27]. However, it should be emphasized that the distribution of adiposity (fat storage tissue) may be more important to hepatic steatosis than the total adipose mass [6,35]. In particular, visceral adipose mass is the most important factor for the development of hepatic steatosis in both Asians and Europeans, independent of the total adipose mass and BMI [6,35–37].

In addition to metabolic disorders, a number of other risk factors for NAFLD have been identified from Chinese studies [6,14–16,18,19,26]. These include advancing age, male gender (see below), lower education, physical inactivity, daytime somnolence, high fat intake, overeating, recent weight gain, expanding waist circumference, and family history of MetS components and cardiovascular disease [6,14–16,18,19,26]. On the other hand, there is no association between current cigarette smoking or history of chronic viral hepatitis and NAFLD in Chinese patients [18,38]. Recently, a study from Guangdong Province showed that single nucleotide polymorphisms (SNPs) in the gene for peroxisome proliferator-activated receptor- γ (PPAR- γ), but not its co-activator-1 α (PGC-1 α), is associated with individual susceptibility to NAFLD, possibly through the adiponectin pathway [39]. However, another similar study from Hong Kong failed to identify any association between adiponectin and TNF- α gene polymorphisms and biopsy-proven NAFLD, or with significant hepatic fibrosis in this disorder [40].

As with many other features of MetS, advancing age is associated with increasing prevalence of NAFLD in Chinese population [6,14,18,19]. But female gender is not a risk for NAFLD, in fact men outnumber women in most of the published series [6,14,15]. A bimodal age distribution has been observed in several studies [18,19,27]. As for cardiovascular disease, the peak prevalence of NAFLD occurs earlier (40–49 years) in men than in women (over 50 years), see Fig. 1 [6,18].

Contrary to the numerous risk factors, there are a few protective factors against NAFLD in China that have been described. These include more exercise, working under moderate stress, and, seemingly paradoxically, mild alcohol consumption [26]. In these studies, mild alcohol consumption was defined as average alcohol

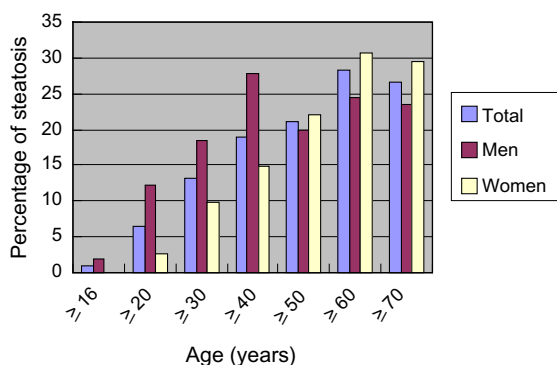


Fig. 1. Prevalence of fatty liver among 3175 Shanghai adults. Adapted from Fan et al. [6,18], with permission.

intake of less than 10 g *per day* [23,26]. In other research studies, mild to moderate alcohol consumption was found to be associated with a lower prevalence of hyperinsulinemia and MetS [41–43]. Thus, light alcohol drinking could reduce the incidence of NAFLD by improving insulin resistance. The reason for the apparent protective of moderate stress against NAFLD has not yet been explored, but sympathetic nervous system activity and increased basal metabolic rate would be theoretical possibilities.

5. Clinical settings of Chinese patients with NAFLD

Although NAFLD appears to be the commonest cause of elevated ALT and liver injury in healthy Chinese adults [23,25], it currently comprises a low proportion of cases of chronic liver disease in both inpatient and outpatient series from tertiary referral hospitals [44,45]. Thus, the records of the liver clinic of Queen Mary Hospital (Hong Kong) show that chronic hepatitis B (CHB) remains the most common reason for referral with chronic liver disease (89% of cases), followed by CHC (5%), alcoholic liver disease (1.7%) and NAFLD (1.5%) [44]. Among cases of chronic hepatitis of unknown etiology, the prevalence of biopsy-proven NASH was found to be 16% (15/97) [45], and in patients with morbid obesity it was 34% (54/160) [13].

In accord with international experience, most patients with NAFLD have no symptoms specific to liver disease, the full range of histological manifestations of NAFLD has been demonstrated in Chinese patients, from simple steatosis, through NASH to cirrhosis [28,46–48]. As in North America, Australia and Europe, T2DM is the most important predictor of severe histological disease, and of more frequently abnormal liver function tests among patients with NAFLD [6,27,34,47,49]. However, the histological severity of steatohepatitis and fibrosis are generally mild in most Chinese patients with biopsy-proven NAFLD, and bridging fibrosis or cirrhosis have seldom been found

in Chinese liver biopsy samples [13,28,45–50]. This phenomenon might be partly due to the relatively short duration and possibly mild degree of the underlying obesity and related metabolic disorders in Chinese patients with NAFLD at initial liver biopsy. NAFLD-related decompensated cirrhosis and HCC does not yet appear to have been reported from the China mainland or Hong Kong, and only one case of esophageal variceal bleeding arising from NAFLD-related cirrhosis has been reported from Taiwan [51].

The natural history of NAFLD globally is currently difficult to assess, but there is mounting evidence that some patients may eventually develop cirrhosis and HCC [8]. In the only available paired biopsy study of NAFLD in Hong Kong [47], 9 patients (53%) had progressive disease with worsening of fibrosis score, but no patient developed hepatic decompensation or HCC after a median follow up of 6 years. This is a short follow-up for this slowly progressive, relapsing and resulting disorder. What may be more salient is the risk of metabolic disorders in Chinese people with steatosis; seven patients (41%) of the Hong Kong study cohort developed hypertension or T2DM during follow-up[47], revealing the importance of diagnosing NAFLD for prevention and early detection of these metabolic and cardiovascular disorders.

As an indolent form of chronic liver disease, NAFLD may be even less important than primary biliary cirrhosis in Chinese [52], but it need to be appreciated that patients with NAFLD are not expected to develop complications of cirrhosis until late in life [8]. To date, prospective studies in Chinese are too short in duration to exclude late liver complications of NAFLD. Being a recent phenomenon in Chinese hepatology, large, long-term prospective cohort studies, ideally with paired liver biopsy samples, are required to define the natural history and impact of NAFLD for causing serious significant chronic liver disease. The contribution this could make to the HCC burden in Chinese patients also require further study, as both obesity and T2DM increase risk of HCC for CHB and CHC [6,53]. On the other hand, although serum ALT levels often decrease over time in patients with NAFLD followed for up to 6 years, a significant proportion develop dyslipidemia, IGT/T2DM or hypertension soon after the diagnosis of NAFLD, *even* in once non-obese individuals [54]. Thus, the importance of NAFLD may not only be as a liver disease, but more particularly as a predictor, or even an early mediator of T2DM and MetS [55,56].

6. NAFLD and chronic viral hepatitis in China

Over half a billion of the world's population is chronically infected with HBV and hepatitis C virus

(HCV) [2]. China alone accounts for more than two-thirds of the world's cases with chronic HBV infection [2,7]. However, only a proportion of these individuals will develop CHB or CHC, which are progressive liver diseases [2,7]. It is therefore critical to identify which factors contribute to accelerated liver injury and a poor outcome [57,58]. In patients with CHC, hepatic steatosis is one such variable associated with cirrhosis and HCC [57]. It is well known that hepatic steatosis is a histological feature in approximately 50% of patients with CHC. HCV genotypes 2 and 3 directly induce hepatic steatosis, whereas insulin resistance plays a key role in genotypes 1 and 4 HCV infection [57]. The prevalence of non-alcoholic steatosis by ultrasonography in HCV genotype 3 infection was significantly higher than that of other genotypes (39% *vs.* 11%) in 98 Chinese patients with CHC [59]. Moreover, steatosis and host obesity were associated with reduced sustained viral response (SVR) to antiviral therapy according to univariate analysis [59]. The level of plasma insulin and HOMA-IR appeared to be independent factors for predicting SVR in this small cohort [59]. Since the prevalence of HCV infection in the Chinese urban population is low and has been stable over the past 10 years [60,61], chronic HCV infection could not be attribute to the increased prevalence of steatosis in China.

In contrast to CHC, steatosis in persons with CHB is a reflection of the host metabolic profile; it does not correlate with viral factor (such as hepatitis B e antigen status or HBV DNA titer). The prevalence of histological steatosis is relatively low, being 37% among a total of 849 patients with CHB from seven studies outside of China [58]. However, persons with significant alcohol intake were not excluded in some of these studies. According to one study from Taiwan, the prevalence of CHB in morbid obesity patients was 16% (26/160), of which three cases had bridging fibrosis and/or cirrhosis, but no cirrhosis was found in the NASH group without HBV infection [13]. A recent study of 1915 patients with chronic CHB infection from Hangzhou (capital of Zhejiang Province, east China) excluded patients co-infected with HCV, HIV, and alcoholic liver disease. It showed that steatosis by ultrasonography was present in 153 (8%) cases [62], while histological evidence of steatosis was observed in 260 (14%) of liver biopsies [62,63]. Moreover, histological steatosis was associated with metabolic factors not viral ones in Chinese patients with CHB, and it does not appear to influence the severity of hepatic necroinflammatory activity or liver fibrosis stage [63]. Given this strong association with metabolic risk factors, steatosis in patients with CHB should be regarded as NAFLD; and the concurrence of NAFLD in people with chronic HBV infection appears to be no higher than that observed in the general population [1–3,14,18]. According to one early study from Shanghai, the prevalence of NAFLD in participants who were

seropositive for hepatitis B surface antigen (HBsAg) was even less than HBsAg-negative counterparts (8% *vs.* 15%) [26,64]. This could partly be due to an inverse relationship between the presence of MetS and serum HBsAg-positive status in Chinese people [65,66]. Therefore, persons with chronic HBV infection are not a high-risk population for NAFLD. In persons with inactive or low-level chronic HBV infection who also have steatosis and coexisting MetS components, it may be prudent to seek strategies that can reduce liver fat content so as to prevent potentially hazardous metabolic or cardiovascular complications [12,55,56,58].

7. Conclusions

NAFLD is no longer a disease exclusive to developed Western countries. It should be regarded as a global problem. In China, steatosis (~15% urban population) is mainly related to obesity and MetS, not alcohol. Although steatosis is common in patients with CHC, the prevalence of HCV infection in Chinese urban population is low and has remained stable over the past decade. Unlike CHC, steatosis is less common (~14%) in CHB; it is not related directly to the viral infection so much as to the same metabolic factors that cause NAFLD. Therefore, neither alcohol nor chronic viral infection (HBV, HCV) accounts for the rapidly increased prevalence of steatosis in China. With the increasing pandemic of overweight and obesity in the Chinese population, China is likely to harbor an increasing reservoir of patients with NAFLD. The risk factors and clinical settings resemble to those of Caucasian counterparts, although there are substantial differences in the extent of visceral adiposity between Asians and Europeans. NAFLD appears to be associated with insulin resistance and represents the hepatic manifestation of MetS. Not surprisingly, therefore, patients with NAFLD are at high risk of developing of metabolic complications, perhaps much higher than their risk of liver cirrhosis. In contemporary clinical practice, it has become mandatory to evaluate metabolic risk factors in NAFLD patients, and to consider careful surveillance and appropriate lifestyle modification and anti-obesity therapy not only of resultant liver disease, but also of the underlying metabolic complications. Ultimately, though public health initiatives and long-term preventive strategies hold the key to halt or reverse the pandemic of obesity and the possible onset of liver-related complications of NAFLD in China.

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