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New trends on obesity and NAFLD in Asia

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Summary

Traditionally, obesity and its related diseases have been considered a problem in Western countries. However, in the past two decades, urbanisation in many Asian countries has led to a sedentary lifestyle and overnutrition, setting the stage for the epidemic of obesity. This article reviews the epidemiological trend of obesity in Asia, with special emphasis on the emerging condition of non-alcoholic fatty liver disease (NAFLD). Currently, the population prevalence of NAFLD in Asia is around 25%, like many Western countries. While hepatocellular carcinoma and end-stage liver disease secondary to NAFLD remain uncommon, a rising trend has emerged. Around 8–19% of Asians with body mass indexes less than 25 kg/m^2 are also found to have NAFLD, a condition often described as "lean" or "non-obese" NAFLD. Although this condition is generally less severe than that in more obese patients, steatohepatitis and fibrotic disease are well recognized. Central adiposity, insulin resistance and weight gain are major risk factors, and genetic predisposition, such as the *PNPLA3* polymorphism appears to be more important in the development of NAFLD in the non-obese population. Lifestyle modification remains the cornerstone of management for obesity and NAFLD, but few patients can achieve adequate weight reduction and even fewer can maintain the weight in the long run. While pharmacological agents have entered phase III development for steatohepatitis, Asian patients are under-represented in most drug trials. Future studies should define the optimal management of obesity and NAFLD in Asia.

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Key point

Asian people develop type 2 diabetes and cardiovascular disease at a lower body mass index. This should be considered when managing obesity-related disorders in Asians.

Introduction

Obesity and its related diseases (type 2 diabetes, ischaemic heart disease, chronic kidney disease and various cancers) are among the leading causes of death globally. In recent years, non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease, affecting a quarter of the global population.[1] In the United States, it has also become the second leading indication for liver transplantation and the third leading cause of hepatocellular carcinoma (HCC).[2,3]

Long hailed as Western diseases, obesity and NAFLD are now increasingly recognised in the Asian population. Since the epidemiology of NAFLD in China was last reviewed in the *Journal* in 2009,[4] new data on the epidemiology, natural history, pathophysiology and management of obesity and NAFLD in Asia-Pacific countries have emerged. Thus, it is timely to revisit this topic and highlight areas where further research is needed. Similarities and differences between NAFLD in Asia and the West are summarised in Table 1. Asia is a vast continent bounded by the Pacific Ocean to the east, Indian Ocean to the south and Arctic Ocean to the north. The western boundary with Europe is less well defined. Consequently, there is sizeable variation in lifestyle, economic conditions and disease epidemiology within Asia.

What is obesity?

Many studies defined overweight and obesity according to the body mass index (BMI). However, it should be noted that BMI is a crude measurement to facilitate research. According to the World Health Organization (WHO), overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.[5]

To fully grasp the scope of the obesity problem in Asia, one should understand that there are notable differences between the Asian and Western populations in terms of lifestyle, genetics and body composition. In particular, Asians are more likely to have central fat deposition despite having a lower BMI.[6]

This has led some to recommend different BMI cut-off points for the Asian population. However, while the WHO Expert Consultation concluded that the proportion of Asian people at a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing WHO cut-off point for overweight (25 kg/m^2), because of considerable heterogeneity (the cut-off point for observed risk varies from 22–25 kg/m^2 and for high risk varies from 26–31 kg/m^2)[7], the Consultation recommended retaining the same BMI cut-off points for international classification (Table 2).

Although BMI can easily be applied in clinical practice and epidemiological studies, it is an imperfect marker of adiposity because it does not distinguish between muscle and fat mass. In some studies, waist circumference and waist-hip ratio, as markers of central obesity, correlated better with clinical outcomes than BMI.[8] The International Diabetes Federation currently adopts ethnic-specific waist circumference cut-off points to define central obesity and metabolic syndrome (Table 3).[9]

Epidemiology of obesity and NAFLD in Asia

Prevalence and incidence

The WHO Global Health Observatory data in 2014 indicates that globally obesity occurs in 15% of women and 11% of men aged 18 and over.[10] The prevalence of obesity in Asian countries is shown in Fig. 1. There is a strong correlation between NAFLD prevalence and established obesity indices (Table 4). The prevalence of NAFLD, pooled for Asian countries, was estimated to be 27.4% (95% CI 23.3–31.9%).[1] The prevalence of NAFLD in the general Japanese population ranges from 24.6% to 29.7%,[11,12] similar to that in China and Korea. Non-alcoholic steatohepatitis (NASH) is present in at least 20% of obese adults or children, and at least 5% of those who are overweight.[13] The prevalence of NASH, pooled for Asian countries, in biopsy-proven NAFLD patients is 63.5% (95% CI 47.7–76.8%).[1] NASH has emerged as the most common cause of cryptogenic cirrhosis and HCC worldwide. A study from India showed that NAFLD accounts for about 63% of all cryptogenic cirrhosis cases.[14] In Japan, cirrhosis is now the fourth most common cause of death (4.7%) in patients with type 2 diabetes, and HCC is the leading cause of cancer death (8.6%).[15]

Few studies have evaluated the incidence of obesity and NAFLD in Asia. The annual incidence rate of obesity in 2008 was 0.70% in Chinese subjects aged 35 to 74 years old, and the rate was higher in women (0.77%) than men (0.61%), in northern (0.93%) than in southern China (0.51%), and in rural (0.73%) than in urban areas (0.65%).[16] The incidence of obesity in Japanese subjects, aged 40–69 years old and non-obese at baseline, was 0.3–1.1% in men and 0.6–1.2% in women living on the main islands, and 0.8–3.7% in men and 1.4–3.1% in women living on Okinawa, between 1993 and 2003.[17] The pooled regional NAFLD incidence rate estimates in Japan were 52.3 (95% CI 28.3–96.8) per 1,000 person-years in 2005.[1] Among the non-obese Chinese, 8.9% developed NAFLD in five years from 2006 to 2011.[18]

Secular trend

Over the past three decades, changing lifestyles and dietary habits have set the stage for the obesity and NAFLD epidemic in Asia. The global prevalence of obesity more than doubled from 6.4% (95% CI 5.7–7.2%) in 1980 to 12.0% (95% CI 11.5–12.5%) in 2008, largely driven by new cases from Asia,[19] where the prevalence of obesity was historically very low. Recently it has been increasing at an alarming rate, especially in China, Japan, and India.[20] The number of obese Chinese people was below 0.1 million in 1975, rising to 43.2 million in 2014 and accounting for 16.3% of global obesity.[10] The number of obese people in India rose from 0.4 to 9.8 million from 1975 to 2014.[21] In 2014, the prevalence of generalised obesity and abdominal obesity across India ranged from 11.8–31.3% and 18.7–36.1%, respectively.[21] The secular trend for the prevalence of obesity in some Asian countries from 2000 to 2014 is shown in Fig. 2. Meanwhile, NAFLD in Asia is also on the rise. In China, the prevalence of NAFLD was 18.2% in 2000–2006, 20.0% in 2007–2009, and 20.9% in 2010–2013,[22] and the prevalence of fatty liver in patients with biopsy-proven chronic hepatitis B also increased from 8.2% in 2002 to 31.8% in 2011.[23] Even in the rural regions of India, including parts of Maharashtra and Haryana, the prevalence of NAFLD had increased to 28.1% in 2015 and to 30.7% in 2016, respectively.[24,25]

Key point

Urbanisation, sedentary lifestyle and Western diet have contributed to the obesity and NAFLD epidemic in Asia.

Key point

NAFLD currently affects around a quarter of the Asian adult population, and the trend has been increasing in the past two decades.

Regional differences

There may be some regional differences in the phenotypes of obesity and NAFLD. A cross-sectional study across four geographical regions found that South Asian cities had the highest prevalence of generalised obesity and South America had the highest prevalence of abdominal obesity.[26] In obese children, the prevalence of NAFLD also differs by geographic regions: it is lowest in South America and highest in Asia.[27] A recent meta-analysis of adult NAFLD reported higher prevalence in the Middle East and South America, and the lowest in Africa.[1] In addition, there is a striking difference in epidemiology across different Asian countries. The prevalence of obesity ranges from 1% in Timor-Leste to 34% in Qatar (Fig. 1). In China, obesity is more prevalent in the north,[16] and the prevalence of NAFLD varies from 13% in rural areas to 43% in urban areas. Urbanisation and the introduction of a Western diet

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Table 1. NAFLD in Asia and the West.

	Western countries	Asian countries
Prevalence of NAFLD	~25%	~25%
Proportion of NAFLD patients with NASH	20–30%	10–20%
Proportion of NAFLD patients with F3-4 fibrosis	~10%	3–5%
Prevalence of NAFLD in subjects with BMI <25	~10%	7–19%
Risk factors of NAFLD	Obesity and metabolic syndrome, genetics	Obesity and metabolic syndrome May have a stronger genetic component
Applicability of ultrasound elastography	Moderate	High
Response to lifestyle intervention	Yes	Yes
Response to vitamin E and pioglitazone	Yes	Limited data
Response to bariatric surgery	Yes	Limited data

Table 2. International classification of adult underweight, overweight and obesity according to body mass index.[7]

Classification	International	Asian*
Underweight	<18.5	<18.5
Normal range	18.5–24.9	18.5–22.9
Overweight	25.0–29.9	23.0–24.9
Obese class I	30.0–34.9	25.0–29.9
Obese class II	35.0–39.9	≥30.0
Obese class III	≥40.0	

* The classification for adult Asians was proposed by WHO in 2000. However, the WHO Expert Consultation recommended to keep the international classification for all populations in 2004 because of significant heterogeneity across Asian countries. That said, many studies from Asia still adopt the lower body mass index cut-offs according to the proposal in 2000.

have reduced the gap in obesity and NAFLD across regions.[28]

Risk factors of NAFLD in Asia

Sedentary lifestyle

Epidemiological studies have suggested a close relationship between sedentary behaviour and unfavourable metabolic outcomes, including obesity, diabetes, metabolic disorders, and cardiovascular diseases.[29] In particular, even moderate-to-vigorous physical activity cannot fully negate the health risks associated with sedentary behaviours, such as prolonged time watching television.[30] In addition to Western data, Asian studies have revealed a close relationship between a sedentary lifestyle and the risk of NAFLD development. One large cross-sectional study performed in South Korea showed a positive association between prolonged sitting and the prevalence of NAFLD in a middle-aged population.[31]

Sarcopenia

Skeletal muscle is the primary tissue responsible for insulin-mediated glucose disposal.[32] Accordingly, low skeletal muscle mass reduces glucose disposal independently of obesity, explaining the close association between NAFLD and insulin-resistance. Although further prospective longitudinal studies are required, several Korean cross-sectional epidemiological studies recently found that sarcopenia is associated with both NAFLD and NAFLD-related advanced fibrosis, independent of insulin-resistance and obesity status.[33–35] In a recent Japanese study, skeletal muscle mass was negatively associated with the steatotic burden in males with type 2 diabetes.[36] This correlation between sarcopenia and NAFLD was independently confirmed in recent European studies.[37] However, it remains unclear how changes in skeletal muscle mass affect the long-term outcomes of Asians with NAFLD.

Diet

Apart from the effects of individual foods or nutrients, certain dietary patterns (such as the Mediterranean diet) were recently reported to influence NAFLD progression or improvement. Traditional Asian diets contain more vegetables and fish and less red meat and high-fat dairy products than Western diets; this may explain the relatively low prevalence of NAFLD in Asian populations.[38] However, the dietary pattern is changing rapidly in Asia, particularly among the young; the percentages of energy derived from fat have increased over time. Increased fat consumption has been associated with insulin

Table 3. International Diabetes Federation guidance on waist circumference thresholds as a measure of central obesity.[9]

Country/ethnic group	Male	Female
Europids	≥94 cm	≥80 cm
South Asians, Chinese and Japanese	≥90 cm	≥80 cm
South and Central Americans	Use South Asian recommendations until further data	
Sub-Saharan Africans, Eastern Mediterranean and Middle East	Use European recommendations until further data	

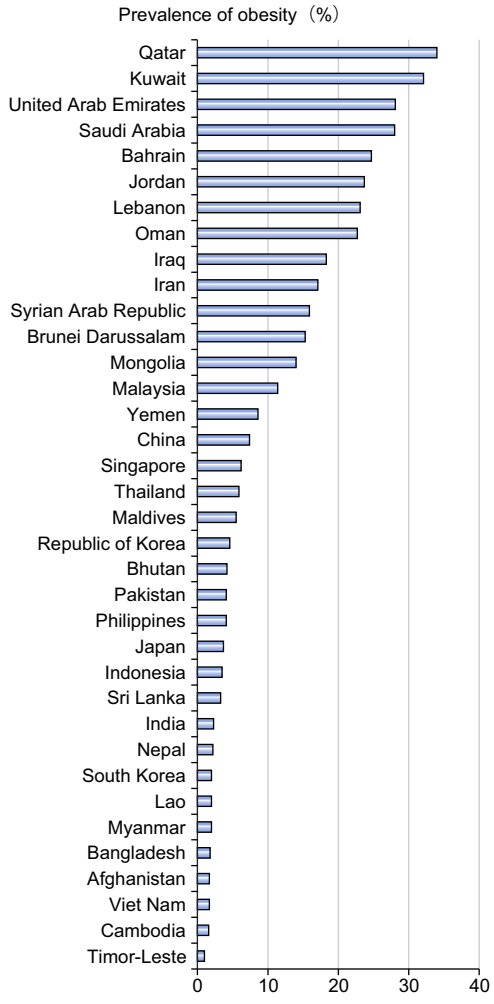

Fig. 1. Prevalence of obesity across Asian countries according to the WHO Global Health Observatory in 2014.[10]

Table 4. Prevalence of NAFLD in Asia.

Setting	Country/region	Prevalence	References
General population			
	China	15–40%	65,75,150
	India	30%	25
	Japan	25–30%	12
	Korea	27%	71
BMI <25 kg/m^2			
	China	8–20%	75,78
	India	7%	76
	Japan	15%	12
	Korea	13%	77
Chronic hepatitis B			
	China	15–50%	126,133
	India	34%	132
	Taiwan	44%	134
	Thailand	38%	136

BMI, body mass index

resistance, postprandial lipid metabolism dysfunction, and NAFLD development or progression.[39,40] In addition, dietary fructose consumption in soft drinks has increased in parallel with the increase in obesity and NAFLD in Asia, as well as in Western countries.[4,41] This is thought to explain the recent increase in obesity and NAFLD.

To date, only a few Asian studies have explored the association between Asian dietary patterns and metabolic outcomes. Dietary supplementation with n-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] or EPA + docosahexaenoic acid);[42,43] a " grains-vegetables" dietary pattern;[44] higher consumption of vegetables, legumes, and fruits;[45] and an elevated intake of vitamin K and vegetables[46] was shown to effectively reduce the risk of NAFLD development in Asian subjects. However, a higher intake of soft drinks and meat; a tendency towards a lower intake of fish rich in omega-3 fatty acids;[47] a low intake of vitamin C, vitamin K, folate, omega-3 fatty acids, and nuts and seeds by males;[46] a high-carbohydrate/sweet dietary pattern in females;[48] and an "animal food" dietary pattern,[44] were all independently associated with an increased risk of NAFLD. Thus, well-designed, large, multinational, prospective studies are required to resolve inconsistencies between studies, which are probably attributable to differences in study design and the ethnicities of the study subjects.

Genetics

Patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) is one of the first genes shown to be associated with NAFLD in a genome-wide association study.[49] The association has since been confirmed in several Asian studies.[50–54] Interestingly, the at risk *PNPLA3* rs738409 GG genotype is found in 13–19% of the general population in Asian studies, compared with 4% in Caucasians, 2% in African Americans and 25% in Hispanics.[49] This may explain the similar NAFLD prevalence between Asian and Western countries despite a difference in metabolic profile. It may also explain why Hispanics are particularly susceptible to NAFLD. In addition, some studies suggest that hepatic iron content may affect oxidative stress and liver injury.[55,56] However, data on the association between *HFE* polymorphism and NAFLD from Asian and Western studies are conflicting.[57,58] In any case, hereditary haemochromatosis is rare in Asia, and the *HFE* mutation is unlikely to play a major role in NAFLD in Asia.

One study found that a single nucleotide polymorphism in the promoter region of the gene encoding apolipoprotein C3 (*APOC3*) was associated with hypertriglyceridaemia, metabolic syndrome, and coronary artery disease,[59] and thus, possibly with NAFLD. However, the role for the *APOC3* polymorphism in NAFLD development remains controversial. One study performed in the United States found that, in healthy non-obese subjects, 38% of Asian-Indian males with *APOC3* variants had NAFLD and exhibited marked insulin-resistance, but no *APOC3* wild-type homozygotes had NAFLD.[60] By

contrast, other studies performed in various ethnic groups suggested that *APOC3* variants did not affect NAFLD development.[61,62] One Chinese study failed to find any significant association between the *APOC3* SNP and the risk of NAFLD development.[50]

Furthermore, an exome-wide association study has identified a variant of the transmembrane 6 superfamily 2 (*TM6SF2*) gene that confers susceptibility to NAFLD.[61] The association was confirmed in Asian cohorts and a subsequent meta-analysis.[63,64] However, only 0.4% of the Chinese population was homozygous for the *TM6SF2* variant, suggesting that it has limited impact at the population level.

Others

In addition to the risk factors described above, older age,[65] male sex,[66] South Asian ethnicities,[67] obstructive sleep apnoea,[68] and metabolic risk factors including diabetes, insulin-resistance, and obesity have been proposed as risk factors for NAFLD progression.[12,69–71] Although low vitamin D levels are significantly associated with NAFLD severity in both Asian and Western studies, the therapeutic role of vitamin D supplementation is unclear.[72] Likewise, the effect of hypothyroidism on NAFLD is unclear.[73,74]

Non-obese NAFLD

Key point

NAFLD is found in 8–19% of non-obese people. The *PNPLA3* gene polymorphism has a greater effect on liver fat in patients without metabolic syndrome.

While NAFLD is strongly associated with obesity and metabolic syndrome, a proportion of NAFLD patients have relatively normal BMI. In population screening studies or health check programmes in apparently healthy subjects, although high BMI was associated with a higher prevalence of NAFLD, 8–19% of subjects with BMI <25 kg/m^2 were found to have NAFLD (Table 4).[12,75–79] Historically, non-obese NAFLD was mostly reported by Asian investigators, likely because of the different meaning of normal BMI in this population. However, according to data from the US National Health and Nutrition Examination Survey III between 1988 and 1994, 10% of Americans with BMI <25 kg/m^2 still had moderate to severe hepatic steatosis on abdominal ultrasonography.[79] However, it is important to note that the term non-obese NAFLD can be misleading, as a significant proportion of these patients have central obesity.

The severity of NAFLD in non-obese patients is a matter of debate. In a retrospective multi-ethnicity cohort study of 1,090 patients with biopsy-proven NAFLD, 125 (12%) had BMI <25 kg/m^2.[80] Surprisingly, subjects with BMI <25 kg/m^2 had more severe histological lobular inflammation and higher mortality (hazard ratio 11.8). Unfortunately, that study was only published in abstract form, precluding thorough examination of patient characteristics and confounding factors.

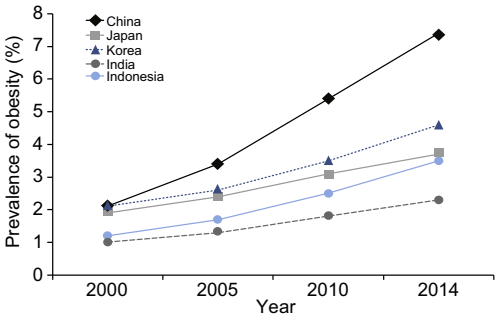

Fig. 2. Secular trend of the prevalence of obesity in Asia from 2000 to 2014.

In contrast, another histological series of 307 patients from Hong Kong did not suggest more severe NAFLD in the non-obese population.[81] Overall, non-obese patients had lower steatosis grade and fibrosis stage, and were less likely to have liver fibrosis (55% *vs.* 80%; p <0.001). Nevertheless, a similar proportion of non-obese and obese patients had NASH (44% *vs.* 52%; p = 0.22) and F3-4 fibrosis (26% *vs.* 28%; p = 0.79). At a median follow-up of 49 months, non-obese and obese patients had a similar rate of adverse clinical events (8.3% *vs.* 11.9%), though death and HCC were only found in obese patients. Although histological cohorts are informative, they only represent a small proportion of all NAFLD patients with different indications for liver biopsy. In a study of 911 community subjects in Hong Kong, 135 of 701 (19%) subjects with BMI <25 kg/m^2 and 127 of 210 (61%) subjects with BMI ≥25 kg/m^2 had fatty liver detected by proton-magnetic resonance spectroscopy.[78] Non-obese subjects with NAFLD were less likely to have increased NAFLD fibrosis score than obese subjects, but a similar proportion of patients in the two groups had increased liver stiffness measurement by transient elastography, asparate aminotransferase-to-alanine aminotransferase ratio, aspartate aminotransferase-to-platelet ratio index (APRI), fibrosis-4 index and the BARD score. Again, this suggests that although non-obese patients may still develop NASH and/or fibrosis, they are not at a higher risk than obese patients.

Despite relatively normal BMI, most non-obese NAFLD patients have other metabolic risk factors. Factors associated with NAFLD in the non-obese population include other markers of adiposity (*e.g.* waist circumference, skin fold thickness and body fat percentage), hyperglycaemia and insulin resistance, dyslipidaemia, high blood pressure, male sex and older age. A Japanese study also showed that some non-obese patients with NAFLD had gained weight since early adulthood.[12] Likewise, a study in Hong Kong using paired proton-magnetic resonance spectroscopy three to five years apart showed that changes in waist circumference and serum triglycerides were the two most important factors

associated with new development of NAFLD in people with baseline BMI <23 kg/m^2.[82] Thus, clinicians should not just focus on the current metabolic profile, but enquire about weight gain over time.

PNPLA3 also correlates with NAFLD in non-obese subjects. In one Chinese study, *PNPLA3* had an even stronger impact on hepatic steatosis in people without metabolic syndrome.[51] However, studies in Caucasians suggest an interaction between *PNPLA3* and visceral adipose tissue.[83,84]

Another uncertainty surrounding non-obese NAFLD is whether the pathophysiology differs from that of NAFLD in obese patients. A metabolomics study revealed changes in lysophosphatidylcholines and phosphatidylcholines in patients with non-obese NAFLD, but it is unclear if such changes are more important in non-obese subjects.[85] Besides, insulin resistance is almost universal in NAFLD patients, even among lean patients and before clinical manifestation of hyperglycaemia.[86] Reduced insulin sensitivity at the adipose tissue increases lipolysis and fatty acid influx to the liver, and enhances very low-density lipoprotein secretion.

Liver-related complications

Like other chronic liver diseases, NAFLD and NASH induce fibrosis progression in some patients, eventually leading to cirrhosis and its complications (Fig. 3). However, because of the close association between NAFLD and metabolic syndrome, most patients die of cardiovascular diseases and cancers rather than liver-related complications. That said, because of the huge number of NAFLD patients, many would still develop liver-related complications even if they only represent a small proportion of all NAFLD patients. Therefore, it is not surprising that NAFLD/NASH has become an important cause of HCC and end-stage liver disease in the Western world.[2,3]

Since NAFLD has not been a research focus in Asia until recently, clinical outcome data are scarce. In a retrospective study of 6,508 Japanese patients with NAFLD diagnosed by ultrasonography, only 16 (0.25%) patients developed HCC during a median follow-up of 5.6 years.[87] In another cohort of 307 patients with biopsy-proven NAFLD in Hong Kong, two (0.65%) developed HCC and one (0.33%) developed hepatorenal syndrome and hepatic encephalopathy at a median follow-up of 49 months.[81] Likewise, in another cohort of 612 patients with clinical indications for cardiac catheterisation and therefore a high metabolic burden, only two (0.33%) patients developed primary liver cancer during 3,679 patient-years of follow-up, and no other patient developed liver decompensation.[88] Taken together, liver-related complications do not appear to be a major problem in Asian NAFLD patients in the short- to intermediate-term. Nonetheless, it takes years if not decades for chronic liver diseases to progress to cirrhosis. Even in the United States, it is only in the past decade that NAFLD has rapidly risen to be an important cause of HCC and end-stage liver disease.[2,3] Besides, economic growth and energy abundance are recent events in many Asian countries, and a significant proportion of the population still live in poverty. As a result, the majority of adult NAFLD patients in Asia have later disease onset than their Caucasian counterparts; this may further explain the low event

Key point

HCC and end-stage liver disease from NAFLD/NASH are uncommon in Asia. This is probably due to later economic development in Asia and therefore shorter disease duration in most patients.

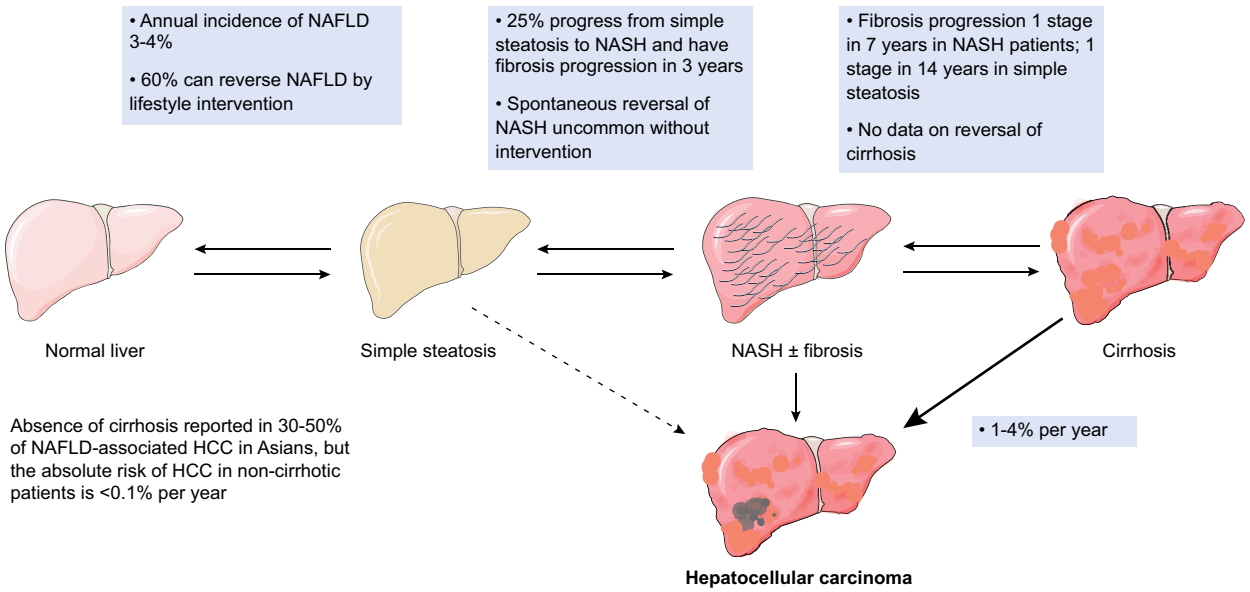

Fig. 3. Natural history of NAFLD according to data from Asia.

rate in Asia. Nonetheless, recent studies have already noted a rising trend in NAFLD-related HCC.[89,90]

Since the natural history of NAFLD is incompletely understood, current regional guidelines only recommend HCC surveillance in patients with cirrhosis.[91–93] However, a small study from Japan suggests that NAFLD-related HCC often develops in the absence of cirrhosis (39% of male patients and 70% of female patients had cirrhosis at the time of HCC).[94] Subsequently, a larger cohort of 1,500 HCC cases in the United States confirmed the finding, with a third of NAFLD-related HCC being non-cirrhotic based on histology, APRI, clinical and radiological features.[95] While the cause of this observation remains unclear, the clinical implication is profound. Screening all NAFLD patients regularly for HCC is impractical. In the longitudinal study by Kawamura *et al.*, the risk of HCC was exceedingly low in NAFLD patients who were non-diabetic or had an APRI of $\leq$1.5.[87] This is a practical approach that deserves to be validated in other cohorts. Furthermore, steatohepatitic HCC has been described by several Asian groups in patients with chronic hepatitis B or C.[96,97] In this condition, the histological features of HCC resemble NASH with large droplet steatosis, ballooning of malignant cells, Mallory-Denk bodies and pericellular fibrosis. It is unclear if this is a unique phenomenon in Asia, but it supports the contribution of the NAFLD/NASH pathway to hepatocarcinogenesis.

Key point

Around a third of NASH-related HCC may develop in a non-cirrhotic liver. Diabetes and non-invasive tests of fibrosis may help define the at-risk population, but confirmation in longitudinal studies is required.

Extrahepatic diseases associated with NAFLD/NASH

A number of Asian studies have demonstrated an association between NAFLD and ischaemic heart disease,[88] obstructive sleep apnoea[98] and colorectal neoplasia.[99] This topic has recently been reviewed and will not be discussed in detail.[100] Although most of these studies corrected for other metabolic factors by multivariable analysis, there might still be residual confounding factors, and a causal relationship between NAFLD and these extrahepatic disorders has not been established. Type 2 diabetes, obesity and the other components of metabolic syndrome are strongly associated with NAFLD in a dose-dependent manner.[65,75]

Management of obesity and NAFLD in Asia

Are these conditions recognised?

Urbanisation, increasing affluence and behavioural changes (physical inactivity and high fat/energy-excessive diet), have led to obesity and NAFLD becoming common in both the developed and the newly industrialised economies of Asia. Efforts should focus primarily on preventing or ameliorating the impact of obesity and NAFLD. Reversing these trends must be a public health priority. Although the region has been a significant contributor to the current state of knowledge, the consequences of obesity, the spectrum of NAFLD and their potential for significant future morbidity and health costs are not widely recognised by the regions' governments, healthcare providers and clinicians. Inadequate awareness still exists among common people and even specialists.[101,102] A large proportion of general practitioners and physicians in many disciplines are not familiar with the official guidelines.[103,104] Therefore, both education for the general population and targeted training programmes for physicians are urgently required in Asia.

Key point

The governments in China and Korea have developed community programmes to curb obesity-related disorders. A multidisciplinary approach is the key to success.

Lifestyle intervention

Weight loss is the most important intervention for obesity and NAFLD. Lifestyle intervention programmes can achieve reductions in liver fat content and resolution of NASH. Asian data support a 7–10% weight loss target, although evidence suggests that up to 40% of individuals with NAFLD can improve with 3–5% weight reduction.[105,106] Several recent Asian studies have also confirmed the role of exercise in reducing liver fat and possibly fibrosis.[107–110] Both aerobic and resistance training are effective; the selection may be based on patients' preference and the likelihood of long-term adherence.[111] However, there are currently no Asian data supporting the hypothesis that NASH can be resolved through lifestyle changes. Combined diet and exercise strategies are more effective in improving liver enzymes levels and histology than either modality alone.[112] A multidisciplinary approach to management is important to ensure motivation and continued participation in intervention programmes.[113] The government plays an important role in addressing lifestyle behaviours and population health, whose involvement comprises surveillance, research, programming, access to healthcare, and guidelines for diet and physical activity.[114] Recently, the Chinese central government announced the "Healthy China 2030" programme to improve health issues. Reducing the risk of chronic disease by promoting a healthier lifestyle is a pivotal component of the programme, of which obesity and type 2 diabetes are the two major targets. Measurements include the creation of a healthcare system that puts a premium on preventive care and community-based health education programmes.[115] Similarly, in Korea, the Seoul Metabolic Syndrome Management (SMESY) programme has been employed as a community-wide, lifestyle modification intervention since 2011, and a recent retrospective study observed temporal associations between the implementation of the SMESY programme and improvements in metabolic disorders.[116] Therefore, a collaboration of government, physicians and

researchers can effectively promote healthy lifestyles and benefit patients with obesity and NAFLD.

Pharmacological treatment

Although lifestyle management is effective and should be encouraged, not all patients can adhere to diet and exercise. Besides, it is difficult for patients with morbid obesity and musculoskeletal disorders to do sufficient exercise. Therefore, pharmacological treatment may be required in some patients. According to current European and American guidelines, vitamin E and pioglitazone may be considered in selected patients with NASH. Obeticholic acid, elafibranor, selonsertib and cenicriviroc have also entered phase III development. However, Asian patients have been under-represented in drug trials for obesity and NASH. Because of notable differences between Asian and Caucasian populations, future studies should involve more Asian patients to inform clinical practice.

Bariatric surgery

By improving obesity and diabetes, bariatric surgery reduces liver fat and is likely to improve all histological lesions of NASH, including fibrosis.[117] It is a cost-effective therapy for NASH patients in all classes of obesity and may even be cost-effective for treating individuals with advanced fibrosis.[118] Bariatric surgery should be considered as a treatment option for metabolic syndrome and type 2 diabetes in Asian patients, if their BMI $>30\ kg/m^2$.[119] A constant increase in the total number of bariatric procedures has also been witnessed in Asia over the past decade, and sleeve gastrectomy has become the most frequently performed procedure in Asia.[120] This may delay progression of liver disease to decompensation and also increase the candidacy for liver transplantation.[121] However, it is premature to consider bariatric surgery an established option for the specific treatment of NASH.

Assessing treatment efficacy

In general practice, it may be sufficient to note changes of anthropometric indices, serum lipids, blood glucose, liver tests, and abdominal ultrasonography during treatment of NAFLD with and without obesity. Depending on availability, the degree of hepatic steatosis and fibrosis stage can be assessed by transient elastography or magnetic resonance imaging-based techniques, as a more sensitive alternative to abdominal ultrasonography. However, these are not sufficient for NASH patients because: (i) liver biopsy remains the gold standard for characterising liver histology in NAFLD and is essential for the diagnosis of NASH,[117,122] (ii) improvement or reversal of steatosis has not been shown to correlate well with reversal of NASH, and (iii) the only legitimate surrogate marker for an improved hepatic outcome is improvement in fibrosis.[123] The therapeutic objective for NASH should be the reversal of liver fibrosis or at least the prevention of worsening fibrosis score with resolution of steatohepatitis. The diagnostic performance of non-invasive tests for monitoring changes in liver fibrosis requires further validation.

Impact of fatty liver and metabolic syndrome on chronic hepatitis B

Hepatitis B virus (HBV) infection is endemic in Asia and is associated with a high risk of HCC development. Recent nationwide HBV immunisation programmes in Asian countries have significantly reduced the seroprevalence of hepatitis B surface antigen (HBsAg) in the younger generation.[124] However, because its seroprevalence remains high in older individuals, HBV infections continue to burden Asian countries.

The prevalence of fatty liver in Asian HBV patients ranges from 14% to 67%[125–137] (Table 4) and is similar to that in Western countries.[138] Several Asian studies have found inverse associations between HBV infection and NAFLD prevalence/incidence.[133,137] In addition, HBV patients are at a reduced risk of metabolic syndrome.[139] A recent meta-analysis of data from 4,100 HBV-infected patients found a strong inverse association between HBV DNA levels and fatty liver in HBV patients, suggesting that HBV infection potentially protects against the development of fatty liver.[140] By contrast, other studies found no correlation between a fatty liver and HBV infection.[126,141] One experimental study even revealed that expression of hepatitis B X protein promoted lipid accumulation in the liver.[142] In addition, the presence of either fatty liver or metabolic syndrome in HBV-infected patients was an independent risk factor for the development of cirrhosis.[143,144] Further studies are warranted to explore the influence of NAFLD on the long-term outcomes of antiviral therapy.

Evidence supporting the association between obesity and HBV-related HCC development is weak. In one study from South Korea, HCC development was not associated with obesity-related factors in patients with chronic HBV infections receiving entecavir.[145] Similarly, obesity alone did not correlate with HCC risk in HBsAg-seropositive patients in one Taiwanese study, but obesity combined with diabetes synergistically enhanced the risk of HCC development in HBV patients (relative risk 12.8).[146] By contrast, recent Asian studies have clearly shown that diabetes may be a potential risk factor for HBV-related HCC development.[147,148] In addition, insulin resistance correlates with HCC risk even in patients without overt metabolic abnormalities.[149]

Key point

While a few agents have entered phase III development for NASH, Asian patients have been under-represented in drug trials. Their response to pharmacological treatment is largely unknown.

Key point

Chronic hepatitis B virus infection is endemic in Asia. The impact of obesity and concomitant fatty liver in this situation remains uncertain, but adverse liver outcomes appear to be largely controlled with antiviral therapy.

Conclusion

A westernized diet and sedentary lifestyle have led to the emergence of obesity and NAFLD in Asia, over the last decade. While HCC and end-stage liver disease secondary to NASH remain uncommon in Asia, these complications take decades to develop, and major changes in the epidemiology and natural history of NAFLD are expected. At present, lifestyle modification remains the most important option for managing obesity and NAFLD. Since Asian patients are under-represented in drug trials for NASH, future studies should take different ethnic groups into consideration to guide treatment options in clinical practice.

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Conflict of interest

Vincent Wong served as an advisory board member for AbbVie, Gilead Sciences and Tobira; a consultant for Janssen, Perspectum Diagnostics and Pfizer; and a speaker for Bristol-Myers Squibb, Echosens and Merck. None of these is related to the content of this article.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All three authors performed literature review, drafted the manuscript, and read and approved the final version of the manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2017.06.003.

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