

REVIEW

What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific?

Jian-Gao Fan,* Toshiji Saibara,[†] Shivakumar Chitturi,[‡] Byong Ik Kim,[§] Joseph J Y Sung,[¶] A Chutaputti** and the Asia-Pacific Working Party for NAFLD¹

*Center for Fatty Liver Disease, Shanghai First People's Hospital, Jiaotong University, Shanghai, China; [†]Department of Gastroenterology and Hepatology, Kochi University, Kochi, Japan; [‡]Gastroenterology and Hepatology Unit, The Canberra Hospital, Canberra, Australia; [§]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea; [¶]Chinese University of Hong Kong, Hong Kong, China; and **Section of Digestive and Liver Diseases, Department of Medicine, Phramongkutklao College of Medicine, Bangkok, Thailand

Key words

fatty liver, metabolic syndrome, non-alcoholic fatty liver disease, obesity, risk factor.

Accepted for publication 10 January 2007.

Correspondence

Professor Jian-Gao Fan, Center for Fatty Liver Disease, Shanghai First People's Hospital, Jiaotong University, Shanghai 200080, China.
Email: fanjg@citiz.net

¹Full composition and affiliations of the Asia-Pacific Working Party for NAFLD are given in reference¹.

Abstract

The risk factors and settings for non-alcoholic fatty liver disease (NAFLD) in Asians are reviewed comprehensively. Based particularly on large community-based studies using ultrasonography, case-control series and prospective longitudinal studies, the prevalence of NAFLD in Asia is between 12% and 24%, depending on age, gender, locality and ethnicity. Further, the prevalence in China and Japan has nearly doubled in the last 10–15 years. A detailed analysis of these data shows that NAFLD risk factors for Asians resemble those in the West for age at presentation, prevalence of type 2 diabetes mellitus (T2DM) and hyperlipidemia. The apparent differences in prevalence of central obesity and overall obesity are related to criteria used to define waist circumference and body mass index (BMI), respectively. The strongest associations are with components of the metabolic syndrome, particularly the combined presence of central obesity and obesity. Non-alcoholic fatty liver disease appears to be associated with long-standing insulin resistance and likely represents the hepatic manifestation of metabolic syndrome. Not surprisingly therefore, Asians with NAFLD are at high risk of developing diabetes and cardiovascular disease. Conversely, metabolic syndrome may precede the diagnosis of NAFLD. The increasing prevalence of obesity, coupled with T2DM, dyslipidemia, hypertension and ultimately metabolic syndrome puts more than half the world's population at risk of developing NAFLD/non-alcoholic steatohepatitis/cirrhosis in the coming decades. Public health initiatives are clearly imperative to halt or reverse the global 'diabesity' pandemic, the underlying basis of NAFLD and metabolic syndrome. In addition, a perspective of NAFLD beyond its hepatic consequences is now warranted; this needs to be considered in relation to management guidelines for affected individuals.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a metabolic disorder originally assumed to be largely confined to residents of affluent, industrialized Western countries;¹ however, obesity and insulin resistance, the common substrates of NAFLD, are not restricted to the West, as witnessed by their increasingly universal distribution.² In particular, there has been an upsurge in obesity-related metabolic syndrome in the Asia-Pacific region, so that in countries such as China, Japan, Korea and probably India, rates of NAFLD are between 12% and 24% of the general population.^{1–5} There are critical differences with respect to the extent of adiposity between Eastern and Western populations; these have important implications for definitions of central and overall obesity, and for metabolic syndrome.^{6–9} In light of these differences, we provide an Asia-Pacific regional perspective of risk factors and settings for NAFLD.

Risk factors for non-alcoholic fatty liver disease

As reviewed elsewhere,^{2,5,10,11} NAFLD is associated with clinical conditions found in the metabolic syndrome including obesity, hypertension, diabetes and dyslipidemia. Indeed, it is likely that NAFLD is the hepatic manifestation of this syndrome, and that insulin resistance is a key factor in disease pathogenesis.^{1,2} Regardless of body mass index (BMI), the presence of type 2 diabetes mellitus (T2DM) significantly increases the risk and severity of NAFLD.¹² Central obesity seems to be an important risk factor for NAFLD, even in patients with a normal body mass index (BMI), and may be the key link with insulin resistance.^{1,10} Likewise, the lipid disorders associated with metabolic syndrome, hypertriglyceridemia rather than hypercholesterolemia, are those found in metabolic syndrome and may increase the risk of NAFLD.¹

Table 1 Prevalence of obesity in Asia using WHO criteria for Asians[†]

Country	Men (%)	Women (%)
China	12	14
Japan	24	20
Malaysia	24	18
Philippines	13	15
Taiwan	18	16
Thailand	17	20

[†]Adapted from International Diabetes Institute.⁶

Obesity

Although BMI and waist circumference can best predict some metabolic disorders, only 2–3% of Asians are classified as obese by current Western criteria for Caucasians (BMI of more than 30 kg/m²).^{6,7} It is now recognized that obesity-related metabolic disorders commence at much lower levels of BMI in Asians.^{6,7} Studies on body fat have shown that Asians have a higher percentage adiposity at a lower BMI than Caucasians.^{6,7} Data from Singapore indicate that for any given percentage of body fat, BMI of Singaporeans is 3 kg/m² lower than that of Caucasians. Studies from Hong Kong Chinese and Asian Indians show that the odds ratio (OR) of clustering metabolic risk factors starts to increase at a BMI of about 23 kg/m². Therefore, the recommended BMI cut-off values for Asians for overweight are 23–25 kg/m², and for obesity more than 25 kg/m², according to the new BMI criteria for Asians by the regional office for Western Pacific Region of World Health Organization (WHO).^{3,4,6,7}

Applying these new criteria presents a very different picture on the prevalence of obesity in Asia, as summarized in Table 1.⁶ There is evidence that these numbers will only worsen with the increasing adoption of a Western lifestyle. Indeed, in China the number of obese subjects has doubled in 10 years.^{8,9} Thus, the first comprehensive national survey in 2004 on diet, nutrition and disease found that among the total Chinese population of about 1.3 billion, an estimated 200 million (15%) are overweight or have obesity, 20 million have diabetes and 160 million have hypertension.^{8,9}

Non-alcoholic fatty liver disease is now recognized as one of the most prevalent manifestations of the obesity-related metabolic syndrome. Although NAFLD and its more severe form, non-alcoholic steatohepatitis (NASH), may develop in non-obese patients, the majority of cases occur in obese or overweight individuals. In a population-based survey from Shanghai, among 661 patients with fatty liver, 611 (92%) had NAFLD, and fatty liver was more strongly associated with obesity than with heavy alcohol use. Compared with the controls, the risk for fatty liver was 3.6-fold higher in heavy drinkers, 12-fold higher in obese people and 17-fold higher in obese drinkers. Indeed, in heavy drinkers, obesity increased the risk for fatty liver by 4.8-fold (95% confidence interval [CI], 1.4–17). Conversely, it is interesting to note that heavy drinking did not significantly increase the risk for fatty liver (OR, 1.50; 95% CI, 0.9–2.6) in obese subjects.¹⁰ These findings are consistent with those of Bellentani *et al.*¹¹ Therefore, NAFLD should now be regarded as a global problem, and Asian countries, in which half the world's population resides, are likely to harbor a significant reservoir of this form of liver disease.¹³

Table 2 Central obesity is strongly associated with steatosis in Japanese[†]

Study group, by obesity and central obesity	OR for steatosis
Controls (normal weight, not centrally obese)	Reference group
Normal weight, centrally obese	1.89
Obese, not centrally obese	2.57
Obese, centrally obese	5.64

[†]Adapted from Hsieh *et al.*¹⁵ Obese was defined as body mass index ≥ 25 kg/m² in both sexes; centrally obese was defined as a ratio of waist to height over 0.5. OR, odds ratio.

Central obesity

It should be emphasized that the distribution of fat may be more important than the total adipose mass. Central obesity is a correlate of visceral adiposity and is more closely linked to insulin resistance, the central event in NASH, than is generalized obesity.¹⁴ Thus, the direct association between abdominal fat and hepatic lipid content is probably accounted for by visceral adiposity. This point is well illustrated by the results of a Japanese survey of over 2500 men, subdivided into four groups by BMI and waist/height measurements (Table 2).¹⁵ As shown in Table 2, the odds ratio for fatty liver was most influenced by central obesity, being 5.6 in those with both overall and central obesity. Therefore, fatty liver can occur in (apparently) 'lean' but centrally obese individuals (Table 2), and its prevalence rises with further degrees of obesity, especially central obesity. An important additional observation of this study was that centrally obese people had much lower levels of physical activity than the others; this underscores the importance of lifestyle in contributing to the obesity epidemic, not simply overeating.¹⁵

Of note, lean NASH patients may have central adiposity. This provides an explanation for the subgroup of non-obese patients who, it has been suggested, represent the lean part of a spectrum of insulin-resistance subjects (frequently of Asian origin) in which genes may play a more critical role in disease pathogenesis. Ethnic difference in proclivity to central adiposity are well recognized.⁷ South Asians, particularly those from the Indian subcontinent, have a particularly high prevalence of central obesity, suggesting that they may be at an increased risk of NAFLD; this has recently been confirmed in North America.^{16,17}

Diabetes mellitus

In addition to obesity, T2DM may be a particularly important risk factor for NAFLD. Non-alcoholic fatty liver disease is the most common chronic liver disease seen in patients with T2DM. Of the 10 leading countries with T2DM (highest proportion of population), five are in Asia (India, China, Pakistan, Indonesia and Japan). It is anticipated that by 2025, nearly 130 of the projected 300 million cases of T2DM worldwide will live in these five countries. Further, an increase in the prevalence of T2DM across the Asia-Pacific region is anticipated; early trends are already

evident. Likewise, traditional hunter–gatherer populations (Australian Aborigines, Nauruan fishermen, Maoris) have already experienced a profound upsurge in the prevalence of T2DM.^{12,18}

Epidemiologic studies have demonstrated that T2DM occurs in 21% to 45% of patients with NAFLD, and approximately an additional 30% have a family history in a first-degree relative.^{1,12,19} Further, the onset of new cases of T2DM among patients with NAFLD during follow up is very high.^{20,21} Diabetic patients with NASH appear to be at risk for more advanced liver disease as several retrospective studies have identified diabetes to be an independent predictor of advanced fibrosis.^{1,12} Younossi *et al.* evaluated this relationship further in a cohort of NAFLD patients identified between 1979 and 1987. Cirrhosis was present in 25% of patients with diabetes compared with 10% of those without diabetes. The diabetic patients tended to be older and had higher serum glucose and triglyceride levels. Mortality in the NAFLD cohort with diabetes was double (57%) that of NAFLD patients without diabetes (27%). The overall risk ratio for liver-related mortality was 23% in the diabetic group.²²

Insulin resistance

It is now recognized that insulin resistance is a universal part of the pathophysiology of NAFLD. Fatty liver itself is an insulin-resistant state, not only in subjects with additional metabolic disorders, but also in lean subjects with normal glucose tolerance, since hepatic fat accumulation can lead specifically to hepatic insulin resistance.^{23–26} Although Asian studies using the euglycemic clamp to measure insulin sensitivity are lacking, there is abundant indirect evidence that insulin resistance underlies the development of NAFLD in this region, as well as in Asian Indians in the United States of America.²⁷ First, insulin resistance-associated metabolic disorders such as central obesity, obesity, impaired glucose tolerance (IGT) or T2DM and hypertriglyceridemia often coexist with NAFLD in Asian patients.

Second, hyperinsulinemia, a correlate of insulin resistance, has been observed in several studies from the Asia–Pacific region.^{28,29} Fasting or postprandial serum insulin levels, or the homeostasis model assessment – insulin resistance (HOMA-IR) have been used to assess insulin resistance. The HOMA-IR is calculated from fasting serum glucose \times serum insulin (both in mmol/L) divided by 22.5. It generally correlates well with standard methods of measuring insulin sensitivity such as the euglycemic clamp technique; exceptions include older patients and those with established diabetes after pancreatic-cell failure has caused serum insulin levels to fall. Studies from Korea, India, Japan and China have demonstrated higher serum insulin and HOMA-IR levels in patients with NAFLD as compared with matched controls. As expected by comparison with European and North American studies, similar findings have been reported from western Sydney in Australia.¹⁹ Further, HOMA-IR has been identified as an independent predictor of NAFLD both in obese and more recently in apparently non-obese persons (BMI < 25 kg/m²). A few studies that have examined adipokine profiles in NAFLD have also confirmed the relationship of NASH/NAFLD with low serum adiponectin levels in Asians;³⁰ however, current data are insufficient to demonstrate a consistent association between any particular type of adipokine profile and histologic severity of NAFLD.²⁸

Table 3 The revised ATP III criteria of metabolic syndrome for the Asian Study[†]

The metabolic syndrome is defined by any three of the following factors	
Central obesity	Waist circumference ≥ 90 cm (M), ≥ 80 cm (W), and/or BMI ≥ 25 kg/m ² in both sexes
Hypertriglyceridemia	Triglycerides ≥ 1.7 mmol/L
Reduced HDL-C	HDL-C < 1.03 mmol/L (M) and < 1.29 mmol/L (W)
Raised blood pressure	Blood pressure $\geq 130/85$ mmHg
Raised fasting plasma glucose	FPG ≥ 5.6 mmol/L or previous diagnosed type 2 diabetes

[†]Adapted from previous studies.^{31–33} Patients receiving treatment for metabolic syndrome components are considered to meet the respective criteria. ATP III, Adult Treatment Panel III; BMI, body mass index; FPG, fasting plasma glucose; HDL-C, high density lipoprotein cholesterol; M, men; W, women.

Metabolic syndrome

The term metabolic syndrome refers to a cluster of cardiovascular risk factors associated with insulin resistance. The prevalence of the syndrome has varied markedly according to several differences in definitions used and the populations studied.⁴ If the National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria are applied to an Asian population, this will underestimate the prevalence of metabolic syndrome in the population at risk.⁴ When the appropriately revised ATP III criteria are used (Table 3), with a lower waist circumference cut-off (90 cm for men, 80 cm for women), it is readily apparent that prevalence rates of the metabolic syndrome in adult Singaporeans, Chinese, Asian Indians and Koreans are comparable to those in Western populations according to the ATP III criteria. For example, among 4723 Singaporeans, decreasing the cut-off for waist circumference increased the crude prevalence of the metabolic syndrome from 12% to 18%. Metabolic syndrome was more common in men (prevalence 21%, vs 16% in women) and Asian Indians (29%) than in Malays (24%) and Chinese (15%).³¹ In Shanghai adults, the prevalence of metabolic syndrome according to the revised definition (with modified waist circumference) was significantly higher than if the ATP III definition was used (15% vs 9.2%).³² Similarly, in an urban Korean population, the rates of metabolic syndrome were 16% in men and 11% in women according to the ATP III definition; but when the waist circumference cut-off is reduced to 90 cm in men and 80 cm in women, the prevalence was 29% and 17% in men and women, respectively.³³ It is also apparent from these data that the cut-off points for central obesity based on waist circumference recommended by International Diabetes Federation (IDF) definition are applicable across the broad Asian population, although more subtle ethnic differences are likely to exist between and within individual populations.

Recently, the age-adjusted prevalence of the metabolic syndrome among 8465 Korean adults according to the criteria of the IDF (waist circumference ≥ 90 cm for men and ≥ 85 cm for women) was reported as 14% in men and 15% in women;³⁴ however, it is considered that the new IDF definition could decrease the prevalence and the risk of vascular events and diabe-

Table 4 The risk of fatty liver increases according to the number of components of metabolic syndrome[†]

Component of metabolic syndrome	Relative risk of fatty liver (95% confidence limits)
Central obesity	33 (14–72)
Diabetes	32 (14–70)
Dyslipidemia	23 (10–50)
Hypertension	23 (11–51)
Metabolic syndrome	39 (18–87)

[†]Adapted from Fan *et al.*³²

tes compared with the revised ATP III definition in Asians.^{35,36} Therefore, the revised ATP III definition (Table 3) has been widely used for Asians studies over the years.

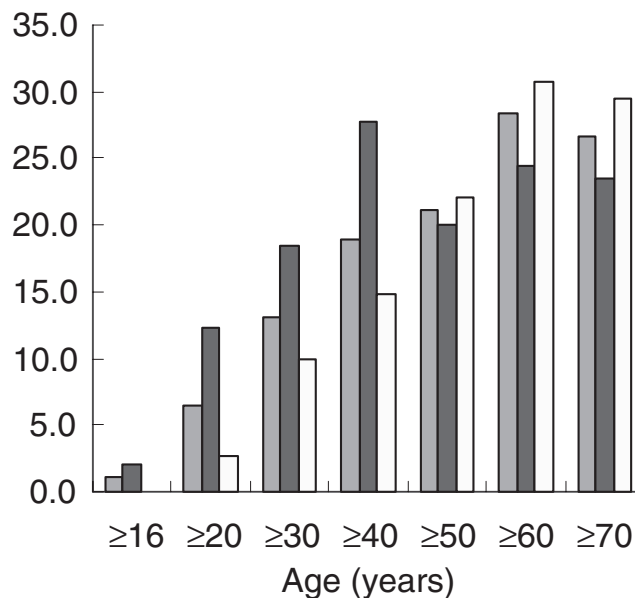
It is now recognized that metabolic syndrome is important in the pathophysiology of NAFLD. In a recent, large cross-sectional study of Shanghai adults, the risk of hepatic steatosis increased exponentially with each addition of the components of the metabolic syndrome. The risk for fatty liver in subjects with one of central obesity, diabetes, dyslipidemia and hypertension increased from 23-fold up to 33-fold (Table 4) compared with controls (subjects with none of these risk factors), whereas the risk for fatty liver in subjects with metabolic syndrome was increased by 39-fold (95% CI, 18–87).³² In addition, the presence of the metabolic syndrome makes it more likely that a patient will have NASH rather than steatosis.^{23–25} Finally, a study from Japan has recently shown that presence of metabolic syndrome greatly increases the risk of developing NAFLD during the next few years, whereas loss of steatosis (by ultrasound) is associated with resolution of metabolic syndrome.³⁷

Other risk factors for non-alcoholic fatty liver disease

In addition to metabolic disorders, a number of other risk factors for NAFLD have been identified from Asian studies. These include advanced age, gender (see below), lower education, physical inactivity, high fat intake, overeating, recent weight gain and expanding waistline, and family history of obesity and/or diabetes, and family history of fatty liver. No close relationship has been observed between current cigarette smoking or chronic viral hepatitis and NAFLD.^{10,13,38}

Age and gender

Although NAFLD may affect people of any age and has been described in most racial groups, in general, increasing age is associated with increasing prevalence of NAFLD. Female gender is not a risk for NAFLD. Men outnumber women in most of the published series from the Asia-Pacific region; however, in two studies, a bimodal age distribution has been observed; the peak prevalence of NAFLD in men occurs earlier (40–49 years) than for women (over 50 years). In women, prevalence peaks once age exceeds 50 years (Fig. 1); this is consistent with experimental evidence that estrogens may be partially protective against steatosis.^{10,13,37,39,40}

**Figure 1** Prevalence of fatty liver among 3175 Shanghai adults, shown as (■) % of population, (■) % of men and (□) % of women. Adapted from Fan *et al.*,¹⁰ with permission.

Risk factors for advanced fibrosis in non-alcoholic fatty liver disease

With respect to predictors of advanced hepatic fibrosis, diabetes has been shown to be a risk factor in some Asian studies, which is in agreement with Western studies.^{1,29,41–43} Additional variables identified as independent markers of fibrotic severity include a platelet count of $\leq 160\,000/\mu\text{L}$, a hepatic necroinflammatory grade of ≥ 2 and aspartate aminotransferase (AST) at least twice the upper limit of normal. Older individuals tend to be overrepresented in cirrhotic cohorts, but age by itself has not been selected in multivariate analyses.^{1,28,29,41–43}

Other variables selected by univariate but not multivariate analyses include female gender, obesity, hypertension and the aspartate aminotransferase : alanine aminotransferase (AST : ALT) ratio. Hepatic iron overload and the presence of hemochromatosis gene mutations (which are rare in Asians) do not correlate with fibrotic severity. Biomarkers of hepatic fibrosis, such as hyaluronic acid level, appear promising and are being evaluated.^{13,28}

Independent risk factors for severe hepatic fibrosis in NASH were assessed in a Japanese study.⁴¹ As expected, prebiopsy cirrhosis-related variables, such as low platelet count and AST : ALT ratio >1 , were selected as independent determinants. All four patients with a low platelet count had cirrhosis; however, the AST : ALT ratio was less specific. Thus, seven of 19 patients with a ratio >1 had only mild hepatic fibrosis, and among those with stage 3 or 4 hepatic fibrosis, only 52% had an AST : ALT ratio >1 . When data were re-analyzed to exclude variables that were a consequence of cirrhosis, age and absence of hyperlipidemia were identified as independent predictors of fibrotic severity. In agreement with Western studies, patients with severe hepatic fibrosis were older than those with milder disease (mean 64 vs

50 years, respectively). Although female gender and diabetes were not selected, women (65%) and patients with T2DM (48%) predominated among those with severe fibrosis in comparison with those with mild fibrosis (45% and 24%, respectively). The non-association of BMI with severe liver fibrosis in this study contrasts to Western reports, and may be related to the differences in defining BMI discussed earlier. In this study,⁴¹ obesity was defined as a BMI > 25 kg/m², in contrast to mean values of BMI up to 37 kg/m² in Western studies. In agreement with Western reports, hepatic siderosis was observed only in 10% of patients in this Japanese study. Moreover, the degree of iron overload was mild and did not correlate with the severity of hepatic fibrosis.⁴¹ In an interesting study from Malaysia, where liver biopsies were performed on a series of patients with NAFLD, multivariate analysis identified male gender and Indian race as predictive factors for severe fibrosis. The latter is interesting in a multiethnic country such as Malaysia where Chinese, Malays and Indians coexist. Indians (South Asians) have been noted to be prone to metabolic syndrome and it may be that they are also more susceptible to more severe forms of NAFLD.²⁹

In a case-control cohort study among Shanghai Bao-Steel Group employees, mean ALT values in NAFLD patients at a median follow up of 6 years were significantly lower compared with the corresponding value at baseline. Moreover, no patients developed complications of cirrhosis during follow up, according to clinical features, liver function tests and ultrasonography.²⁰ This is in line with the results from a study reported by Friis-Liby *et al.* which indicated that NAFLD is associated with only a small risk of progressive liver disease.²¹ In that study,²¹ 19 patients (24%) underwent a liver biopsy in the original diagnostic work-up, and 89% of those fulfilled the criteria for NASH; however, only mild inflammation and early fibrosis were observed; none had cirrhosis. None of those patients with both clinical and histological diagnosis of NAFLD or steatohepatitis developed signs of impaired liver function during follow up in Friis-Liby's study.²¹ Nevertheless, interpretation of these findings is complicated by the fact that the methods of detection might not be sensitive enough to detect development of advanced liver fibrosis or compensated cirrhosis. Recently, Adams *et al.* demonstrated that fibrosis in NAFLD progresses slowly over time, with considerable variability in the rate of progression among patients. Changes of ALT did not parallel changes in fibrosis stages, and diabetic patients with elevated BMI and low fibrosis stage were at risk for higher rates of fibrosis progression.⁴⁴ Others have also shown that presence of NASH, and particularly fibrosis at initial biopsy, indicates more likely progression of chronic liver disease with NAFLD.^{45,46}

Impact of non-alcoholic fatty liver disease on metabolic disorders

Although the association between the metabolic syndrome and NAFLD is well known, the temporal relationship between the development of metabolic syndrome and steatosis is not fully characterized. Most previous reports are of the existence of established metabolic disorders at the time of NAFLD diagnosis; however, NAFLD is not *always* present in obese and diabetic patients at initial diagnosis of those disorders. Conversely, among patients diagnosed with NAFLD, the time required for develop-

ment of central obesity, overall obesity, hyperglycemia, dyslipidemia and/or hypertension is also unclear.

In a recent case-control cohort study from Shanghai employees with NAFLD diagnosed by ultrasonography, the mean levels of and prevalence of various features of metabolic disorders in the fatty liver group were higher than those in controls both at baseline and at 6 years follow up. Although the prevalence of many indices of metabolic disorders increased over time in both groups, such changes were more obvious in the fatty liver group. As a result, the incidence rates of obesity, hypertension, hyperlipidemia, glucose intolerance or T2DM, and multiple metabolic disorders were significantly higher in the fatty liver group than controls at the end of follow up. Moreover, NAFLD was closely associated with the onset of newly diagnosed metabolic disorders, even among non-obese subjects.²⁰ A similar result was observed by Friis-Liby *et al.*; most patients with NAFLD developed metabolic problems soon after diagnosis.²¹ In addition, a cross-sectional survey among Shanghai adults found that fatty liver appears to be a good predictor for the clustering of metabolic risk factors. Compared with central obesity and obesity, NAFLD had the highest frequency of clustering, greater specificity, higher positive predictive value and most attributable risk as a percentage for detecting risk factor clustering in both men and women.³² This is in line with the results of studies by Kim *et al.* among Koreans,^{47,48} which indicate that NAFLD is closely associated with metabolic disorders, even in non-obese and non-diabetic subjects, and that NAFLD can be considered an early predictor of metabolic disorders, particularly in the normal-weight population. Finally, a prospective observational study from Hamaguchi *et al.* suggests that the metabolic syndrome is a strong predictor of NAFLD. In that study, at baseline, 812 of 4401 (18%) participants had NAFLD. During the mean follow-up period of 414 days (SD, 128 days), the authors observed 308 new cases (10%) of NAFLD among 3147 participants who were disease-free at baseline and who completed a second examination. Regression of NAFLD was found in 113 (16%) of 704 participants who had the disease at baseline and who completed a second examination. Men and women who met the criteria for the metabolic syndrome at baseline were more likely to develop the disease during follow up (adjusted OR, 4.00 [95% CI, 2.63–6.08] and 11.20 [95% CI, 4.85–25.87], respectively). Non-alcoholic fatty liver disease was less likely to regress in those participants with the metabolic syndrome at baseline.³⁷ The pathogenesis of metabolic complications among patients with NAFLD and their separate and interactive influence on patient survival still need to be elucidated.

Recently, Adams *et al.* reported that mortality among community-diagnosed NAFLD patients was higher than the general population, and is associated with older age, fasting hyperglycemia and cirrhosis.⁴⁹ Although liver-related death was a major cause of mortality compared with non-affected controls, the absolute risk was low. Dam-Larsen *et al.* found that non-alcoholic steatosis alone has a benign course with progression to cirrhosis occurring in one of 170 patients (0.6%) over a 20-year period.⁵⁰ However, Brea *et al.* demonstrated that NAFLD was an independent risk factor for carotid artery atherosclerosis.⁵¹ Likewise, Villanova *et al.* found that endothelial dysfunction and the 10-year probability of cardiovascular events in NAFLD patients were moderately increased compared with controls.⁵² In addition, Ekstedt *et al.* reported that survival of NAFLD patients was lower

than a matched reference population, mainly because of higher mortality from cardiovascular disorders; there was only a trend towards higher liver-related mortality among NAFLD patients.⁵³ Therefore, NAFLD might not merely be the hepatic manifestation of metabolic syndrome, but could itself directly promote the occurrence and development of metabolic problems. Relationships between steatosis, hepatic and peripheral insulin resistance have been suggested by Petersen *et al.*,¹⁶ and reviewed elsewhere.⁵⁴ Whatever these pathogenic relationships, the key point is that NAFLD is itself an insulin-resistant state. The clinical implication is that patients with NAFLD should be screened regularly for metabolic disorders and related complications, as discussed in the review by Chen *et al.*^{55–57}

Conclusions and future directions

In summary, the risk factors and settings for NAFLD in Asians resemble their Western counterparts with respect to age at presentation, prevalence of diabetes and hyperlipidemia. The differences in the prevalence of central obesity and overall obesity are related to the criteria used to define waist circumference and BMI. There is strong evidence for a major increase in NAFLD prevalence during the last 15 years. The increasing prevalence of obesity, coupled with diabetes, dyslipidemia, hypertension and ultimately the metabolic syndrome puts a very large population (more than 3 billion) at risk of developing NAFLD/NASH in the coming decades. Non-alcoholic fatty liver disease appears to be associated with long-standing insulin resistance, and likely represents the hepatic manifestation of the metabolic syndrome. All these diseases have insulin resistance as a common factor, and are associated with atherosclerosis and cardiovascular risk. Thus, although criteria for the diagnosis of central obesity and overall obesity are different across racial groups, assessment for all features of the metabolic syndrome and related events is mandatory and helpful as a basis for practical management of NAFLD. The simultaneous identification and appropriate treatment of the components of the metabolic syndrome is crucial to reduce hepatic as well as cardiovascular morbidity and mortality.

Future studies should continue to focus both on the similarities and highlight differences in the presentation of NAFLD across this vast, ethnically diverse and socioeconomically variable region. A perspective of NAFLD beyond its hepatic consequences is also needed. Because the importance of the metabolic syndrome is primarily due to a high risk of cardiovascular diseases among those with the syndrome, NAFLD should only be considered a constituent of the syndrome if it increases risk of cardiovascular diseases, for which there is limited evidence. Further studies are needed to evaluate the impact of NAFLD on the well-established obesity- and diabetes-related risks of cardiovascular diseases and malignancy. Finally, public health initiatives are imperative to halt or reverse the 'diabesity' epidemic, the underlying basis of NAFLD.

References

- Angulo P. Nonalcoholic fatty liver disease. *N. Engl. J. Med.* 2002; **346**: 1221–31.
- Williams R. Global challenges in liver disease. *Hepatology* 2006; **44**: 521–6.
- Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am. J. Med.* 2006; **119**: 812–19.
- Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The metabolic syndrome: a global public health problem and a new definition. *J. Atheroscler. Thromb.* 2005; **12**: 295–300.
- Farrell GC, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43** (2 Suppl. 1): S99–112.
- International Diabetes Institute. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment*. Melbourne: Health Communications Australia, 2000.
- Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. *Obes. Rev.* 2002; **3**: 141–6.
- Wu YF. Overweight and obesity in China. The once lean giant has a weight problem that is increasing rapidly. *BMJ* 2006; **19**: 362–3.
- Gu DF, Reynolds K, Wu XG *et al.* Prevalence of the metabolic syndrome and overweight among adults in China. *Lancet* 2005; **365**: 1398–405.
- Fan JG, Zhu J, Li XJ *et al.* Prevalence of and risk factors for fatty liver in a general population of Shanghai, China. *J. Hepatol.* 2005; **43**: 508–14.
- Bellentani S, Saccoccio G, Masutti F *et al.* Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann. Intern. Med.* 2000; **132**: 112–17.
- Harrison SA. Liver disease in patients with diabetes mellitus. *J. Clin. Gastroenterol.* 2006; **40**: 68–76.
- Farrell GC. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? *J. Gastroenterol. Hepatol.* 2003; **18**: 124–38.
- Omagari K, Kadokawa Y, Masuda J *et al.* Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J. Gastroenterol. Hepatol.* 2002; **17**: 1098–105.
- Hsieh SD, Yoshinaga H, Muto T, Sakurai Y, Kossaka K. Health risks among Japanese men with moderate body index. *Int. J. Obes. Relat. Metab. Disord.* 2000; **24**: 358–62.
- Petersen KF, Dufour S, Feng J *et al.* Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. *Proc. Natl Acad. Sci USA.* 2006; **103**: 18273–7.
- Fall CHD. Non-industrialised countries and affluence. *J. R. Soc. Med.* 2001; **60**: 33–50.
- King H, Aubert R, Herman W. Global burden of diabetes, 1995–2005: prevalence, numerical estimates and projections. *Diabetes Care* 1998; **21**: 1414–31.
- Chitturi S, Abeygunasekera S, Farrell GC *et al.* NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology* 2002; **35**: 373–9.
- Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. Effects of nonalcoholic fatty liver disease on the development of metabolic disorders. *J. Gastroenterol. Hepatol.* 22 (in press).
- Friis-Liby I, Aldenborg F, Jerlstad P, Rundstrom K, Bjornsson E. High prevalence of the metabolic complication in patients with non-alcoholic fatty liver disease. *Scand. J. Gastroenterol.* 2004; **39**: 864–9.
- Younossi ZM, Gramlich T, Matteoni CA *et al.* Nonalcoholic fatty liver disease in patients with type 2 diabetes. *Clin. Gastroenterol. Hepatol.* 2004; **2**: 262–5.
- Marchesini G, Bugianesi E, Forlani G *et al.* Non-alcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology* 2003; **37**: 917–23.
- Marchesini G, Brizi M, Bianchi G *et al.* Nonalcoholic fatty liver disease. A feature of the metabolic syndrome. *Diabetes* 2001; **50**: 1844–50.

- 25 Marchesini G, Brizi M, Morselli-Labate AM *et al.* Association of nonalcoholic fatty liver disease with insulin resistance. *Am. J. Med.* 1999; **107**: 450–55.
- 26 Petersen KF, Shulman GI. Etiology of insulin resistance. *Am. J. Med.* 2006; **119** (5 Suppl. 1): S10–16.
- 27 Petersen KF, Dufour S, Feng J *et al.* Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. *Proc. Natl. Acad. Sci. USA* 2006; **103**: 18273–7.
- 28 Farrell GC, George J, Hall PM, McCullough AJ, eds. *Fatty Liver Disease; NASH and Related Disorders*. Maldon, MA: Blackwell Publishing, 2005.
- 29 Malik A, Cheah PL, Hilmi IN, Chan SP, Goh KL. Non-alcoholic fatty liver disease in Malaysia: a demographic, anthropometric, metabolic and histological study. *Chin. J. Dig. Dis.* 2007; **8**: 58–64.
- 30 Wong VW, Hui AY, Tsans SW *et al.* Metabolic and adipokine profile of Chinese patients with nonalcoholic fatty liver disease. *Clin. Gastroenterol. Hepatol.* 2006; **4**: 1154–61.
- 31 Tan CE, Chew SK, Ma S, Tai ES, Wai D. Can we apply the National Cholesterol Education Program Adult Treatment Panel Definition of the metabolic syndrome to Asians? *Diabetes Care* 2004; **27**: 1182–6.
- 32 Fan JG, Zhu J, Li XJ *et al.* Fatty liver and the metabolic syndrome among Shanghai adults. *J. Gastroenterol. Hepatol.* 2005; **20**: 1825–32.
- 33 Oh JY, Sung YA, Hong YS, Barrett-Connor E. Prevalence and factor analysis of metabolic syndrome in an urban Korean population. *Diabetes Care* 2004; **27**: 2027–32.
- 34 Park HS, Han JH, Lee SY, Kim DJ, Kim SE. Prevalence of the metabolic syndrome among Korean adults according to the criteria of the International Diabetes Federation. *Diabetes Care* 2006; **29**: 933–4.
- 35 Adams RJ, Grande ED, Appleton S *et al.* Population comparison of the two clinical approaches to the metabolic syndrome. Implications of the new International Diabetes Federation consensus definition. *Diabetes Care* 2005; **28**: 2777–9.
- 36 Saelly CH, Aczel S, Koch L *et al.* Adult Treatment Panel III. 2001 but not International Diabetes Federation 2005 criteria of the metabolic syndrome predict clinical cardiovascular events in subjects who underwent coronary angiography. *Diabetes Care* 2006; **29**: 901–7.
- 37 Hamaguchi M, Kojima T, Takeda N *et al.* The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann. Intern. Med.* 2005; **143**: 722–8.
- 38 Fan JG, Zeng MD, Li JQ *et al.* Analysis of risk factors for fatty liver. *Zhonghua Yixue Zazhi* 1998; **32**: 189.
- 39 Park SH, Jeon WK, Kim SH *et al.* Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. *J. Gastroenterol. Hepatol.* 2006; **21** (1 Pt 1): 138–43.
- 40 Shen L, Fan JG, Shao Y *et al.* Prevalence of nonalcoholic fatty liver among administrative officers in Shanghai: an epidemiological survey. *World J. Gastroenterol.* 2003; **9**: 1106–10.
- 41 Shimada M, Hashimoto E, Kaneda H, Noguchi S, Hayashi N. Non-alcoholic steatohepatitis: risk factors for liver fibrosis. *Hepatology Res.* 2002; **24**: 429–38.
- 42 Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with non-alcoholic steatohepatitis. *Hepatology* 1999; **30**: 1356–62.
- 43 Ratziu V, Giral P, Charlotte F *et al.* Liver fibrosis in overweight patients. *Gastroenterology* 2000; **118**: 1117–23.
- 44 Adams LA, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J. Hepatol.* 2005; **42**: 132–8.
- 45 Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology* 1999; **116**: 1413–19.
- 46 Sanyal AJ, Banas C, Sargeant C *et al.* Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology* 2006; **43**: 682–9.
- 47 Kim HJ, Kim HJ, Lee KE *et al.* Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch. Intern. Med.* 2004; **164**: 2195–75.
- 48 Park SH, Jeon WK, Kim SH *et al.* Prevalence and risk factors of non-alcoholic fatty liver disease among Korean adults. *J. Gastroenterol. Hepatol.* 2006; **21**: 138–43.
- 49 Adams LA, Lymp JF, St Sauver J *et al.* The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology* 2005; **129**: 113–21.
- 50 Dam-Larsen S, Franzmann MB, Christoffersen P, Larsen K, Becker U, Bendtsen F. Histological characteristics and prognosis in patients with fatty liver. *Scand. J. Gastroenterol.* 2005; **40**: 460–67.
- 51 Brea A, Mosquera D, Martin E, Arizti A, Cordero JL, Ros E. Nonalcoholic fatty liver disease is associated with carotid atherosclerosis: a case-control study. *Arterioscler. Thromb. Vasc. Biol.* 2005; **25**: 1045–50.
- 52 Villanova N, Moscatiello S, Ramilli S *et al.* Endothelial dysfunction and cardiovascular risk profile in nonalcoholic fatty liver disease. *Hepatology* 2005; **24**: 473–80.
- 53 Ekstedt M, Franzen LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Survival and causes of death in patients with elevated liver enzymes associated with non-alcoholic fatty liver disease. *J. Hepatol.* 2006; **44** (Suppl. 2): S40–1.
- 54 Larter CZ, Farrell GC. Insulin resistance, adiponectin, cytokines in nonalcoholic steatohepatitis: which is the best target to treat? *J. Hepatol.* 2006; **44**: 253–61.
- 55 Targher G, Bertolini L, Poli F, Rodella S, Scala L *et al.* Nonalcoholic fatty liver disease and risk of future cardiovascular events among type 2 diabetic patients. *Diabetes* 2005; **53**: 3541–6.
- 56 Volzke H, Robinson DM, Kleine V *et al.* Hepatic steatosis is associated with an increased risk of carotid atherosclerosis. *World J. Gastroenterol.* 2005; **11**: 1848–53.
- 57 Chan HLY, de Silva HJ, Leung NWY *et al.* How should we manage patients with non-alcoholic fatty liver disease in 2007? *J. Gastroenterol. Hepatol.* 2007; **22**: 801–8.