Epidemiology of NAFLD in North America and Europe

Prevalence The epidemiology of NAFLD in the USA and Canada (North America) is similar, and the rates from these two countries can be interchangeable [1–7]. The data from the USA estimates that 27–34 % of the general population have NAFLD while 75–92 % of the morbidly obese individuals have NAFLD [8]. Additionally, prevalence of NAFLD patients with type 2 diabetes is high with a prevalence rate estimated to be between 60 and 70 % [9]. As the prevalence of obesity and metabolic conditions increased over the past two decades, the prevalence of NAFLD continues to rise [6, 10].

In the USA, there are ethnic differences for the prevalence of NAFLD. In fact, the prevalence of NAFLD among European-Americans is 33 %, while it is 45 % in Hispanic Americans and 24 % in African Americans [3–7]. These data seem consistent from different studies from the USA reporting the highest prevalence of NAFLD in Hispanic Americans and lowest prevalence in African Americans [3–7].

Similar to North America, the prevalence of NAFLD in Europe is also very high. In fact, one-fourth of the general European population may have NAFLD with the prevalence rates reported as low as 8 % from Romania and up to 45 % from Greece [7, 11–13]. Although not entirely clear, the wide range of prevalence rates is most likely due to the NAFLD definitions and the diagnostic modalities used [14, 15].

Again, similar to the US patients with diabetes, prevalence of NAFLD in the European patients with diabetes is also high ranging between 42.6 and 69.5 % [16]. Furthermore, the prevalence of NAFLD in patients who meet the criteria for metabolic syndrome rate has been estimated to be about 79 % [17] (Table 2.1).

Incidence There is no precise data on the incidence rates for NAFLD in North America or Europe. This is partly due to the fact that NAFLD is usually a silent disease discovered incidentally. Nevertheless, given that the prevalence of obesity in adult Americans has almost doubled since the early 1960s (1962—48 % vs. 2010—75 %), the incidence of NAFLD in the USA has almost certainly increased [32, 33].
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Price, 2014</td>
<td>USA</td>
<td>HIV+ and HIV− men in the Multicenter AIDS Cohort Study.</td>
<td>N=719 n=254 HIV-men n=465 HIV + men</td>
<td>Overall-15 % HIV− = 19 % HIV+ = 13 %</td>
<td>Fatty liver was defined as a liver-to-spleen attenuation ratio &lt; 1 on non-contrast computed tomography (CT).</td>
<td>[18]</td>
</tr>
<tr>
<td>World Gastroenterology Organization Global Guidelines, 2012</td>
<td>USA</td>
<td>A representative sample of the US population</td>
<td>NA</td>
<td>General population 27–34 % Morbid obesity 75–92 % European-Americans 33 % Hispanic Americans 45 % African Americans 24 %</td>
<td>A variety of sources not reported</td>
<td>[19]</td>
</tr>
<tr>
<td>Browning, 2004</td>
<td>USA</td>
<td>Dallas Heart Study</td>
<td>734 (non Hispanic white only)</td>
<td>33 %</td>
<td>Hepatic triglyceride content &gt; 5.5 %</td>
<td>[5]</td>
</tr>
<tr>
<td>Ioannou, 2006</td>
<td>USA</td>
<td>NHANES (1999–2002)</td>
<td>6823</td>
<td>9 %</td>
<td>ALT &gt; 43 U/L or AST &gt; 40 U/L</td>
<td>[22]</td>
</tr>
<tr>
<td>Giday, 2006</td>
<td>USA</td>
<td>Local clinic data</td>
<td>320</td>
<td>19 %</td>
<td>Liver biopsies</td>
<td>[24]</td>
</tr>
<tr>
<td>Williams, 2011</td>
<td>USA</td>
<td>Cohort of middle age patients at large hospital</td>
<td>328</td>
<td>46 %</td>
<td>Ultrasound</td>
<td>[25]</td>
</tr>
<tr>
<td>Bedogni, 2005</td>
<td>Italy</td>
<td>Dionysos Project</td>
<td>3345</td>
<td>20 %</td>
<td>Ultrasound</td>
<td>[26]</td>
</tr>
<tr>
<td>Radu, 2008</td>
<td>Romania</td>
<td>Cohort of hospitalized patients</td>
<td>3005</td>
<td>20 %</td>
<td>Ultrasound</td>
<td>[27]</td>
</tr>
<tr>
<td>Gastaldelli et al., 2009</td>
<td>Europe</td>
<td>A representative sample of the European population</td>
<td>NA</td>
<td>20–30 %</td>
<td>A variety of sources not reported</td>
<td>[1, 19]</td>
</tr>
<tr>
<td>Zois, 2010</td>
<td>Greece</td>
<td>Subjects aged 3–98 years old</td>
<td>498</td>
<td>31 %</td>
<td>Autopsy</td>
<td>[30]</td>
</tr>
<tr>
<td>Caballeria, 2010</td>
<td>Spain</td>
<td>Individuals aged 15–85 years old</td>
<td>773</td>
<td>33.4 %</td>
<td>Ultrasound</td>
<td>[31]</td>
</tr>
</tbody>
</table>
Parallel to the increase of obesity in North America, the rate of obesity in European countries has also increased. In 2008, the rate of obesity throughout Europe was estimated to be 15.5% with another 34.6% of general population recorded as being overweight [19]. It is important to note that there may be some geographic difference in rates of obesity in Europe. In fact, the prevalence of obesity was found to be highest in Hungary (28.5%), the UK (26.1%), and Ireland (23.0%) followed by Malta (22.7%), Luxembourg (22.7%), and the Czech Republic (21%) with lowest rates being reported from Romania (8.5%), Switzerland (8.7%), Norway (10%), and Italy (10.2%). Given that these prevalence rates for obesity throughout Europe are increasing, the incidence of NAFLD in Europe is expected to rise. Despite this paucity of data on the incidence of NAFLD in North America and Europe, the rates from outside these two areas have been estimated to be around 10% per year [34].

**Risk Factors**

**Age, Gender, and Ethnicity**

Clinical characteristic of patients with NAFLD are similar in North America and Europe [31, 33–43]. The average age of NAFLD patients in North America and Europe is 40–50 years old. Contrary to the initial description of NASH, the majority (60–70%) of patients with NAFLD in the USA are male. Similar gender distribution is reported from Europe except for specific countries such as Lithuania where most of the NAFLD patients are reported to be female [10, 35].

As previously mentioned, most (90%) patients with NAFLD are found to be overweight or obese. Additionally, age may be associated not only with the development of NAFLD but also its progressive form, NASH [36]. In one particular study, patients who developed NASH were younger, were of Hispanic origin, and had components of metabolic syndrome [37]. These findings were supported in another study where NAFLD/NASH patients were more likely to be male (P<0.0001); have lower hip-to-waist ratios (P=0.03); were less likely to be African American (P=0.06); and had higher levels of alanine aminotransferase (ALT; P<0.0001), aspartate aminotransferase (AST; P<0.0001), and serum triglycerides (P=0.0154), but lower levels of high-density lipoprotein cholesterol (P<0.0001). In this study, patients with NAFLD who had moderate to severe fibrosis were older (P=0.0245), were more likely to be male (P=0.0189), were Caucasian (P=0.0382), have diabetes mellitus (P=0.0238), have hypertension (P=0.0375), and have a lower hip-to-waist ratio (P=0.0077). Furthermore, they had higher serum AST (P<0.0001) and ALT (P<0.0001) levels. After multivariate analysis for predicting moderate to severe fibrosis in NAFLD patients, the significant independent variables were male sex, Caucasian ethnicity, diabetes mellitus, and increased AST and ALT levels (model P value<0.0001). Based on these findings the investigators developed a predictive model to help clinicians identify patients at high risk for developing or of having advanced fibrosis. This model had a positive predictive value 31.4% (23.9–39.8%) and a negative predictive value of 91.0% (86.7–94.3%). It is important to note that presence of diabetes alone increased the odds of having advanced fibrosis 25.41%. This risk incrementally increased as other metabolic syndrome components were added. For example, for patients who had diabetes and hypertension, their risk for moderate to advanced fibrosis was 26.32%, and if patients also had central obesity (lower hip-to-waist ratio), their odds increased to 26.67% [38]. It is important to note that in addition to the high prevalence of NAFLD and NAFLD-related fibrosis in diabetics, NAFLD patients with diabetes are also at risk for increased liver-related mortality [38–44].

Although NAFLD may be more common in men, female patients with polycystic ovary syndrome (PCOS) have an increased risk for NAFLD. Researchers have found that the prevalence of both polycystic ovary syndrome
and nonalcoholic fatty liver disease rises proportionally to the degree of insulin resistance and the mass of adipose tissue present [45]. The mechanism of action that may cause this association or in fact may actually increase the progression of NAFLD in women with PCOS may be reflected by significantly elevated levels of caspase-cleaved CK18 (M30) suggesting a more proapoptotic environment. This, in addition to the hyperandrogenic state present in PCOS, may cause a suppression of the LDLR (plays a major role in the clearance of apoB- and apoE-containing lipoproteins) receptor sites both in adipocytes and in the liver creating a prolongation of the half-life of VLDL and LDL thereby causing steatogenic effects [45, 46].

In summary, NAFLD in North America and Europe is associated with obesity, diabetes, and other component of metabolic syndrome, including PCOS in female patients. Additionally, being male, being younger (<50 years old), and being of Hispanic descent in the USA increase the risk of having NAFLD. Although lean NAFLD can be seen in these parts of the world, they represent a much smaller cohort with a different clinical profile [37].

BMI, Obesity, and NAFLD

As noted previously, risk factors for the development of NAFLD reported from North America and Europe include components of the metabolic syndrome (obesity, dyslipidemia, hypertension, and diabetes/insulin resistance) [31, 41, 47–51]. In this context, visceral obesity is the most important predictor of outcome in NAFLD. In fact, in one study, visceral adipose tissue (VAT) as measured by computed tomography was shown to be strongly associated with NAFLD [(HR) 2.04:1.23–3.38] [52].

The data confirming the association of NAFLD with obesity come not only from tertiary care center but also from population-based studies [2–7, 9, 11–18, 20–67]. In a study from the USA which included 3056 NHANES participants, NAFLD patients were found to be older with a higher BMI, larger waist circumference, and higher sum of skinfolds and had insulin resistance (HOMA > 3.0) or type 2 diabetes [66].

In Europe, similar risk factors for NAFLD (type 2 diabetes, obesity, hypertension, and dyslipidemia) are reported from Europe. In fact, obesity remains the most prevalent risk factor for NAFLD in Europe with 65–90% in patients with NAFLD being obese or overweight. Data recently reported from 165,000 adults who were included in the report from the European Commission on Fatty Liver Inhibition of Progress (FLIP) suggested higher BMI, waist circumference, weight gain during adult life, and physical inactivity all will increase the risk of each stage of clinically recognized NAFLD (REF). Furthermore, both arterial hypertension and dyslipidemia were highly prevalent in patients with NAFLD, especially in women [67].

Given the interactive association of NAFLD with obesity, both obesity and NAFLD should be considered as similar complex disorders which are related to the environment and genetic predisposition. The environmental factors influencing obesity and NAFLD are related to dietary intake (both number of calories and composition of these calories), activity, degree of stress, cultural issues, and other potential contributors [68]. The genetic predisposition of NAFLD is very also interesting and will be discussed in detail in subsequent chapters.

As noted previously, it is important to mention that NAFLD in the USA may also be present in nonobese patients. In fact, this type of NAFLD may be more common in Asian countries. In the USA, the prevalence of NAFLD among lean subjects was estimated to be only 3.7%, while this rate was 17.7% in the obese and overweight individuals [37]. Furthermore, the clinical profile of lean patients with NAFLD is also different where the patients tended to be younger, female, and having a decreased likelihood of having insulin resistance and hypercholesterolemia [37].

Insulin Resistance, Metabolic Syndrome, Diabetes, and Cardiovascular Disease in NAFLD

As noted previously, patients having a history of diabetes 2 or insulin resistance, dyslipidemia, and hypertension are at increased risk for the
development of NAFLD. In one study, the risk of having NAFLD was highest for persons with diabetes (OR, 4.16; 95 % CI, 3.24–5.33), followed by presence of metabolic syndrome (OR, 3.97; 95 % CI, 3.26–4.83). Among other components of metabolic syndrome, central obesity was associated with highest odds for presence of NAFLD (OR, 3.41; 95 % CI, 2.77–4.20) as well as severity of NAFLD (OR, 5.58; 95 % CI, 3.86–8.06). The more component of metabolic syndrome, the higher the risk of NAFLD. In fact, the odds of having NAFLD when three components were present was 9.49 (95 % CI, 5.67–15.90), and when five components were present, the odds was 24.05 (95 % CI, 12.73–45.45) [49].

Given the common risk factors between NAFLD and cardiovascular diseases (CVD), there are increasing reports for higher rates of CVD and CV mortality in NAFLD [1, 49, 69]. A recent study investigating the relationship of NAFLD and cardiovascular disease found that the odds for having a carotid intima–media thickness [cIMT]>0.8 mm and/or presence of plaques in obese patients with NAFLD was 5.96 (95 % CI, 1.60–22.25; p=0.008) in men and 8.26 (95 % CI, 4.02–16.99; p<0.001) in women [69]. In addition to high rate of CVD, there is also an increased rate of CV mortality. Although liver disease has been reported as the third leading cause of death among persons with NAFLD, cardiovascular disease and malignancy are the two top causes of death in NAFLD patients [34]. In one particular long-term follow-up study (mean follow up time of 18.5 years), approximately 60 % of the patients with NAFLD had died with the most frequent cause of death cited as coronary artery disease (30 %), followed by nonliver malignancy (18 %) and then liver-related mortality including hepatocellular carcinoma (15 %) [38, 44].

The strong association of DM and metabolic syndrome with NAFLD has also been reported from Europe. In a prospective study of 230 patients from nine centers, metabolic syndrome was found in the majority of patients (53 %) with 54 % of the patients being male with a mean age of 49.4 ±13.9 years and a mean BMI of 30.6 ±4.6 kg/m². In 16 % of the patients, undiagnosed diabetes was discovered. For the patients (51 %) who had a liver biopsy, fibrotic staging was significantly more severe in patients with metabolic syndrome (2.43±1.25 vs. 1.73±1.18, p<0.001). A subgroup of patients with GGT>5×ULN were significantly older (55.9 vs. 47.64 years, p=0.02), were more frequently diabetic (53 % vs. 23 %, p=0.01), and had more advanced fibrosis (3.42 vs. 1.08, p=0.0080 [41].

Another interesting study from Europe was initiated in Italy. The Italian Society for the Study of Atherosclerosis (SISA) in 2005 started a research project aimed to study NAFLD. Using ultrasound (US) in nondiabetic subjects, the researchers set out to determine the prevalence of NAFLD, its associated risk factors and prevalence of hypertransaminasemia, and its possible determinants. NAFLD prevalence was 0.78. Their initial results showed that men with hepatic steatosis (as compared to men without steatosis) were younger (P<0.05) and had higher triglycerides (P<0.03), higher homeostasis model assessment insulin resistance (HOMA-R) (P<0.003), and increased visceral fat thickness (P<0.0001). Furthermore, women with steatosis showed higher triglycerides (P<0.05), HOMA-R (P<0.04), VFT (P<0.0001), and younger age (P<0.05). Multivariate analyses found that visceral fat thickness (P<0.0001), HOMA-R (P<0.02), and triglyceride to HDL ratio (P<0.05) were associated with the severity of NAFLD. Age (P<0.05), log ratio of triglycerides (P<0.005), and visceral fat thickness (P<0.01) were also associated with higher ALT. The prevalence of steatosis was reported to be the highest reported in patients with metabolic syndrome. These investigators concluded that due to the exclusion of severely obese and diabetic patients, their findings highlight the prominent role that alterations of lipid metabolism play in the pathogenesis of NAFLD [17].

Finally, in a recent study from Finland, the prevalence of NAFLD in young Finnish was 29 % in overweight/obese and 5 % in normal weight individuals. The independent correlates were waist circumference, ALT, BMI, male gender, triglycerides, systolic blood pressure, and insulin resistance [70].
Diet and Physical Activity

Although there seems to be a genetic component to the predisposition to NAFLD, diet and activity play a major role. It seems the Western diet high in calories and refined sugar and fructose may play a role in the development of obesity and associated NAFLD. Nevertheless, systematic assessment of diet and activity at the population level in the USA is scarce [71–82].

Other dietary components may also play a role. In one large population-based study using 4 cycles of NHANES data from 2001 to 2008, investigators studied dietary intake questionnaires which listed 62 nutritional components. Univariate analysis found that 38 % of the nutritional components were significantly different between patients with NAFLD and those without NAFLD where patients with NAFLD. After multivariate analysis adjusting for demographic confounders (age, gender, ethnicity), Hispanic race, being male, being obese (BMI > 30), and drinking less caffeine were associated with NAFLD. Although the issue is controversial and the mechanism is not entirely clear, drinking caffeine in the form of coffee actually seems to have a protective effect on the development of NAFLD. This is possibly due to the suppressive effect that coffee has on hyperglycemia by improving insulin sensitivity through the reduction of inflammatory cytokine expression [71, 72].

It is important to note that diet can have an impact both by being responsible for the development of central obesity as well as a direct effect on the inflammatory environment of patients with NAFLD. In fact, one of the most exciting areas of research in NAFLD is the contribution of visceral adipose tissue (VAT) to the development of NAFLD. In fact, the white adipose tissue of VAT is thought to be an endocrine organ that produces adipokines and cytokines responsible for the development of an inflammatory milieu contributing to pathogenesis of NASH, CVD, and other complications of visceral obesity [73]. In addition to VAT being responsible for the inflammatory milieu of NAFLD, there is also some contribution of diet itself on these proinflammatory fat cytokine/chemokine expression within the liver. Animal studies have suggested that diets high in saturated fat, fructose, and cholesterol as well as a specific combination of carbohydrates and fats (starch/oleate) set off a cascade of molecular metabolic derangements including insulin resistance and activation of the miRNA resulting in a more severe form of NAFLD or NASH [74–76]. In addition to adipocytokines, oxidative stress also plays a major role in the development of NAFLD. Recent findings suggest that the extent of hepatocyte ballooning reflect the severity of oxidative DNA damage and accumulation of DNA methylation in NAFLD [77, 78]. In fact, the impact of diet on the oxidative stress cycle has been suggested [78, 79]. Diet can influence microRNA which is involved in the pathogenesis of NAFLD. In fact, animals exposed to a high fat diet showed a dysregulation of miRNA-451 leading to development of NAFLD and fibrosis [77, 78, 80, 81]. All of these mechanisms may be related to the “additional” effect of diet on the development and progressive nature of NAFLD.

In regard to physical activity, patients with NAFLD seem to have low activity levels compared to controls. In fact, patients with both NAFLD and diabetes experienced the lowest level of physical activity [82].

In summary, NAFLD is associated with components of metabolic syndrome. Although genetic predisposition probably plays a role, it only explains a small portion of the increased risk. In this context, the influences of environmental factors are significantly more important. Metabolic syndrome is quite frequent in the general population, although its prevalence varies considerably according to the criteria used for its definition. Additionally, metabolic syndrome is associated with NAFLD, with the WHO definition being the best to determine its presence, probably because of the inclusion of insulin resistance as a main component. Unification of criteria for metabolic syndrome is needed to adequately compare its prevalence and relationship with NAFLD in different population groups [31].
Epidemiology of NAFLD in Asia

Nonalcoholic fatty liver disease (NAFLD) is an emerging health-care priority in Asia [83–85]. This has a potential impact not only for the emerging liver disease burden in this region but also as a broader public health issue in view of the association of NAFLD with the other metabolic syndrome (MS)-linked noncommunicable diseases (NCD)—obesity, diabetes, and atherosclerotic cardiovascular disease. These countries are in a state of health-care transition with the emergence of a new set of public health priorities that have MS as the unifying factor. NAFLD and the other NCDs are key determinants in this changing disease burden scenario that have implications on global health [86].

Socioeconomic affluence and changes in lifestyle influence NAFLD prevalence in a population. The Asian countries, with their large population, are passing through a period of rapid economic growth and shift of focus in labor policy from a dominant physical to one that depend on knowledge capital and foster physical inactivity. An increasing GDP in these nations is paralleled by a rising body mass index (BMI)—the most widely used surrogate of obesity—in an almost linear relationship to GDP growth [87, 88]. An expanded body fat mass and insulin resistance (IR) are the hallmarks of each of these different MS-linked conditions which frequently coexist, although one may antedate the other [89]. In the light of all these, it is imperative that epidemiology of NAFLD be studied in the context of a broader systemic disease perspective, rather than as a liver disease only.

Overall, NAFLD prevalence in this most populous region of the world is high and is increasing over time. There are several particular features of NAFLD in Asia that need specific mention.

Firstly, Asians have also been shown to have an increased propensity to the adverse clinical outcomes in MS-linked noncommunicable diseases (NCD) including coronary atherosclerosis, diabetes, and hepatic steatosis than other ethnic groups in general [90, 91].

Secondly, Asian people often develop NAFLD, metabolic syndrome, and diabetes in the context of anthropometric parameters, usually measured as BMI, that are considered subthreshold as health risks in Western populations. As a consequence, a different set of BMI and waist circumference cutoffs have been proposed as correlative with MS-linked health risks, including NAFLD, among the Asians [92–94].

Thirdly, the contribution of NAFLD in overall liver disease burden in this region has to be seen in the background of an already existing high prevalence of chronic viral hepatitis and a spiraling increase in per capita alcohol consumption in the general population of the region. Synergism in liver disease progression among various etiologies does exist, and this add further complexities in assessment of impact of NAFLD in the emerging liver disease burden in Asia and the Middle East [95–97].

Fourthly, Asian population groups are ethnically diverse. In addition, there are national as well as regional imbalances in socioeconomic development and cultural changes in this region—each of which influences the heterogeneity of the available data of NAFLD epidemiology that are available from Asia. The study design—characteristics of the population sample and the methodology for diagnosis of NAFLD—also differs significantly across studies. Despite these, the available data provide an assessment of NAFLD epidemiology in Asia and the Middle East with fair precision and depict the changes happening over time.

Prevalence

Most of the available epidemiological studies in NAFLD from Asia are ultrasound based and hence detect prevalence of hepatic steatosis alone initially, correlating it with anthropometric, biochemical, and demographic features of the population (Table 2.2). A more detailed workup, including measurement of liver stiffness—(continued attenuation parameter based quantification of liver fat, CT scan and liver biopsy) has been carried out in a few of these studies for better precision and characterization of liver disease status. A more robust radiological approach was based
Table 2.2 Prevalence of NAFLD in Asian countries

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Population</th>
<th>Sample size (n)</th>
<th>Proportion of nonobese among NAFLD subjects</th>
<th>Prevalence of NAFL&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Prevalence of MS/diabetes among NAFLD persons</th>
<th>Mode of diagnosis</th>
<th>Ref. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fan et al., 2005</td>
<td>Shanghai, China</td>
<td>General population (urban)</td>
<td>3175</td>
<td>NR</td>
<td>611 (19.24 %)</td>
<td>NR</td>
<td>US</td>
<td>[98]</td>
</tr>
<tr>
<td>Wong et al., 2012</td>
<td>Hong Kong, China</td>
<td>General population (urban)</td>
<td>922</td>
<td>NR</td>
<td>264 (28.6 %)</td>
<td>125 (47.34 %)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>MRS</td>
<td>[99]</td>
</tr>
<tr>
<td>Chen et al., 2006</td>
<td>Taiwan</td>
<td>General population (rural)</td>
<td>3245</td>
<td>61 (16.39 %)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>372 (11.5 %)</td>
<td>346 (93 %)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>US</td>
<td>[100]</td>
</tr>
<tr>
<td>Park et al., 2006</td>
<td>Korea</td>
<td>Hospital OPD</td>
<td>6648</td>
<td>419 (33.79 %)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1240 (16.1 %)</td>
<td>234 (18.87 %)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>US</td>
<td>[101]</td>
</tr>
<tr>
<td>Omagari et al., 2002</td>
<td>Nagasaki, Japan</td>
<td>Hospital OPD</td>
<td>3432</td>
<td>141 (44 %)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>319 (9.3 %)</td>
<td>47 (14.7 %)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>US</td>
<td>[102]</td>
</tr>
<tr>
<td>Jimba et al., 2005</td>
<td>Japan</td>
<td>Hospital health checkup</td>
<td>1950</td>
<td>NR</td>
<td>566 (29 %)</td>
<td>(10.95 %)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>US</td>
<td>[103]</td>
</tr>
<tr>
<td>Amarapurkar et al., 2007</td>
<td>Mumbai, India</td>
<td>Selected population (railway colonies)</td>
<td>1168</td>
<td>48 %&lt;sup&gt;c&lt;/sup&gt;</td>
<td>16.6 %</td>
<td>22 %&lt;sup&gt;d&lt;/sup&gt;</td>
<td>US</td>
<td>[104]</td>
</tr>
<tr>
<td>Das et al., 2010</td>
<td>West Bengal, India</td>
<td>General population (rural)</td>
<td>1911</td>
<td>90 (54 %)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>167 (8.7 %)</td>
<td>43 (26 %)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>US and CT</td>
<td>[105]</td>
</tr>
<tr>
<td>Vendhan et al., 2014</td>
<td>Chennai, India</td>
<td>General population (urban)</td>
<td>541</td>
<td>48 (27.74 %)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>173 (32 %)</td>
<td>NR</td>
<td>US</td>
<td>[106]</td>
</tr>
<tr>
<td>Dassanayake et al., 2009</td>
<td>Sri Lanka</td>
<td>General population (urban)</td>
<td>2985</td>
<td>305 (31 %)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>974 (32.6 %)</td>
<td>(49.17 %)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>US</td>
<td>[107]</td>
</tr>
<tr>
<td>Niaz et al., 2011</td>
<td>Karachi, Pakistan</td>
<td>Tertiary care hospital</td>
<td>952</td>
<td>NR</td>
<td>129 (13.6 %)</td>
<td>NR</td>
<td>ALT and US</td>
<td>[108]</td>
</tr>
</tbody>
</table>

<sup>a</sup>Unadjusted prevalence  
<sup>b</sup>Prevalence of metabolic syndrome  
<sup>c</sup>Nonobese defined as BMI <25 kg/m<sup>2</sup>  
<sup>d</sup>Prevalence of abnormal Fasting blood glucose  
<sup>e</sup>Nonobese defined as BMI <23 kg/m<sup>2</sup> and waist circumference <80 cm (female)/<90 cm (male)  
<sup>f</sup>Nonobese defined as BMI <23 kg/m<sup>2</sup>  

US ultrasound, MRS magnetic resonance spectroscopy, CT computed tomography, NR not reported
on MR spectroscopic quantitative estimation of hepatic triglycerides in two studies from Hong Kong. The major variables for study quality were the stringency methods adopted in selection of the study population to remove bias and the method of estimating NAFLD since the majority of the studies included select populations from those attending clinics or from the workplace [8, 84, 109]. There have also been well-planned general population-based studies from India, China, Taiwan, Hong Kong, Korea, and Japan that have used standard sampling strategies with stratifications [98–106, 108, 110–117].

While the strength of the studies differ, NAFLD prevalence in Asia is high (15–20 %) and is increasing over time [84, 118, 119]. There is wide variation in NAFLD prevalence. In general, the prevalence is higher in select, clinic-based populations and lower in the general population studies and higher in urban than rural population studies (Table 2.2). Far Eastern countries (China, Korea, Hong Kong, and Japan) report a higher prevalence in the population than South Asian countries (India, Sri Lanka).

In Asia, the largest number of epidemiological studies is available from China where the prevalence of NAFLD is 20 % (6–38 %). Similar prevalence estimates are available from Japan (15 %), Korea (16–22 %), Hong Kong (Proton MR spectroscopy—27 %), and Taiwan. Data from India is more diverse as are the quality of the reported studies (8–30 %). The prevalence is at least 10 % of the population. Data from Sri Lanka, Malaysia, and Indonesia also indicate that ultrasound prevalence of NAFLD is around 15–20 % of the general population [107, 120–122].

Temporal trends of BMI over the past three decades indicate a progressive global upslope that is marked in the Far East, but is comparatively flat in South Asia [87]. NAFLD has also shown a similar increase in prevalence in the last three decades at least in China and Japan, from where data is available [94, 123]. Of greater importance in Asia is the fact that at least 15–20 % of NAFLD subjects (as high as 54 % in one study) may have a BMI that is within the normal limits for clinical risk, although subtle alterations in markers of increased fat mass in the body may be present. Waist circumference and waist–hip ratio has been shown to be a more useful marker of obesity and metabolic risk including NAFLD correlations among these “metabolically obese normal weight (MONW),” variably called “nonobese”/“lean” NAFLD subjects [37, 124–139].

### Incidence

Despite the fairly large body of data on the prevalence of NAFLD from the Asian population, information on incidence (new-onset NAFLD in people previously free from it over a given time period) is relatively scarce (Table 2.3). However, there are a few well-designed population cohort follow-up studies that report an annual incidence of 3–5 % and most importantly point out the dynamic nature of the process of hepatic steatosis, documenting resolution or regression in another 5 % of subjects. Weight gain, even within the normal range, with increments in BMI and other markers of adiposity along with presence and worsening of MS markers had consistently been shown to be associated with NAFLD incidence in Asian population. Incident fatty liver is often associated with new development of hypertension, ALT increments occur in people who develop incident NAFLD, and there is evidence that weight loss can reverse this dynamic state of hepatic steatosis.

While prevalence and incidence of NAFLD in the adult population increase with aging, a greater concern is the rapid increase of childhood obesity and NAFLD in Asian countries. The prevalence of obesity among children and adolescents is increasing in most Asian countries, and this might occur at a more rapid pace than that in the West. NAFLD–NASH in children is important not only as a liver disease burden but also as an important predictive determinant for development of vascular—endothelial risk in the Asian population, later in life. Reports of NAFLD prevalence among children and adolescents in Asia (Japan, Korea) and the Middle East (Iran, and Egypt) vary between 2.8 % and 15 % in cross-sectional studies. NAFLD in children increases with age and BMI, is more prevalent among boys
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Country</th>
<th>Population</th>
<th>Sample size (n)</th>
<th>Follow-up period</th>
<th>Incidence of NAFL (%)</th>
<th>Mode of diagnosis</th>
<th>Risk factors for new NAFLD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong et al., 2015</td>
<td>Hong Kong, China</td>
<td>General population (urban)</td>
<td>565</td>
<td>47 (34–60) months</td>
<td>78 (13.8 %); 13.5 % at 3–5 yr</td>
<td>MRS</td>
<td>Increase in WC and TG</td>
</tr>
<tr>
<td>Hamaguchi et al., 2005</td>
<td>Japan</td>
<td>Hospital health checkup</td>
<td>3147</td>
<td>414±128 days</td>
<td>308 (10 %)</td>
<td>US</td>
<td>Presence of MS at baseline</td>
</tr>
<tr>
<td>Xu et al., 2013</td>
<td>China</td>
<td>Nonobese subjects</td>
<td>5562</td>
<td>5 years</td>
<td>494 (8.8 %)</td>
<td>US</td>
<td>Age, gender, BMI, WC, TG, HDL, serum uric acid, Hb, and platelet count</td>
</tr>
<tr>
<td>Sung et al., 2014</td>
<td>South Korea</td>
<td>Hospital health checkup</td>
<td>11448</td>
<td>5 years (retrospective)</td>
<td>1418 (12.38 %)</td>
<td>US</td>
<td>Associated with new-onset hypertension</td>
</tr>
<tr>
<td>Donghee Kim et al., 2014</td>
<td>Korea</td>
<td>General population</td>
<td>1375</td>
<td>5 years</td>
<td>288 (20.9 %)</td>
<td>US</td>
<td>Increase in visceral adipose tissue</td>
</tr>
<tr>
<td>Pankaj Singh et al., 2014</td>
<td>West Bengal, India</td>
<td>Nonobese subjects in general population (rural)</td>
<td>83</td>
<td>5 years</td>
<td>26 (31 %); 62.65 per 1000 person-year</td>
<td>US</td>
<td>Higher degree of adiposity at baseline and increase over time</td>
</tr>
</tbody>
</table>

*US ultrasound, MRS magnetic resonance spectroscopy, WC waist circumference, TG triglyceride, BMI body mass index, Hb hemoglobin
*Nonobese defined as BMI <25 Kg/m²
*Nonobese defined as BMI <23 Kg/m² and waist circumference <80 cm (female)/<90 cm (male)
than girls, has a similar distribution of central adiposity like their adult counterparts, and can lead to significant liver disease. Overnutrition with high-calorie, low-nutrient diet, and physical inactivity are factors associated with the prevalence of pediatric and adolescent NAFLD, while the consequences may be felt in terms of an increasing liver disease burden as well as diabetes and cardio-metabolic risk in the future.

As mentioned previously, most individuals with NAFLD are obese. In fact, obesity, measured by standard criteria for BMI and waist circumference along with its ethnicity-specific modifications, is undoubtedly the most significant association of NAFLD. However, it has emerged that a varying proportion of NAFLD subjects (15–21%, up to 75% in one study from India), from Asia, do not have obesity (BMI <25), despite having similar metabolic abnormalities (MS and IR) seen classically in obesity-associated NAFLD. A differential distribution of body fat with expansion of visceral adipose tissue compartment, recent increase in body weight, dietary factors including switch from a traditional carbohydrate-dominant to a cholesterol- and saturated fat-dominant diet, genetic factors predicting unique predispositions, and possibly a different gut microbiome may all be contributing to this subphenotype of NAFLD in Asia [124, 140, 141]. Asians, particularly South Asians, have been shown to have a lower mean insulin sensitivity and higher values of HOMA-IR and hepatic triglycerides for a similar value of BMI as compared with Caucasians, black, and Hispanic people. In addition, adipocytokine profile has been shown to be different in them with higher values of IL-6 indicating a relatively heightened degree of inflammatory activation. In addition, South Asians have larger adipocytes along with higher leptin and lower adiponectin values compared to Caucasians [91]. A similar and related entity described in general MS literature is called metabolically obese normal weight (MONW), and nonobese/lean NAFLD may be the hepatic counterpart of “sick fat cell syndrome” seen in obesity and insulin-resistant states [124]. Despite the anthropometric differences, the very tight link of nonobese NAFLD with insulin resistance and metabolic syndrome suggests that it is not a biologically different entity. Follow-up of a prospective cohort of 155 stringently selected nonobese (BMI <23 Kg/m² and waist circumference <80 cm in female/<90 cm in male) subjects, free from NAFLD at baseline, reported a cumulative 5-year incidence of NAFLD to be 31% [28]. Higher degree of adiposity at baseline and higher increments in anthropometric indices over time were correlated with the development of fatty liver in those without a baseline [133]. In another multiethnic international study that compared “lean” with overweight and obese NAFLD subjects, there was significant phenotypic variability in each category across countries. It appears that ethnicity and regional environmental modifiers might be playing a role in the disease expressions where IR is the key biological determinant [142].

Risk Factors

The risk factors for NAFLD development in Asia, in general, are similar to that of the Western populations. There are subtle differences particularly with regard to the role of central obesity and possible genetic influences in determining the ethnicity-specific differences in body fat partitioning and predisposition to outcomes of NAFLD and its MS-linked cardio-metabolic consequences [143–155].

Age and Gender

In all populations, prevalence of NAFLD along with severity NASH-related liver disease, rate of progression of liver fibrosis, and development of hepatocellular carcinoma (HCC) increases as age advances. MS-linked comorbidities and non-hepatic complications of NAFLD also show increments with age. It is likely that this increased prevalence and severity of IR-linked conditions including NAFLD are due to the age-related decline in insulin sensitivity that has been observed in all populations [93, 109]. In Asia, NAFLD prevalence starts rising after 30 years of
age, with a near linear increase as age group advances. However, these are mostly based on data from adult studies. An important facet of changing NAFLD epidemiology is an increasing prevalence of NAFLD in childhood and adolescence [84, 137]. In the light of this, age-specific prevalence of NAFLD is likely to change in near future with an earlier peak age and a less steep upslope in NAFLD prevalence, changing NAFLD epidemiological features.

Males outnumber females in most studies of NAFLD from Asia, except among postmenopausal women where this difference disappears. Males have also been shown to have a higher degree of NASH, more severe liver fibrosis, and higher mortality in NAFLD, as compared to females. In general, three quarters of NAFLD subjects in some multiethnic studies from the West that included Asians were males, while this proportion is much less (44 %) among Caucasians. Epidemiological studies from Asia also reveal the prevalence of NAFLD to be higher in males than females.

**BMI, Obesity, and NAFLD [88, 92–94]**

Prevalence of NAFLD, as the hepatic manifestation of metabolic syndrome, bears a linear relationship with the prevalence of obesity in the population. BMI, as the most widely used measure of body fatness, correlates well with NAFLD and other MS-linked conditions—diabetes, hypertension, and atherosclerotic vascular disease. In NAFLD, an increasing BMI has been shown to be associated not only with increased prevalence and incidence but also with more severe liver disease—NASH and liver fibrosis. Weight loss with a reduction of BMI has also been shown to improve liver histology and outcome of NAFLD. It has emerged, however, that the strength of BMI as a marker of total adiposity has ethnicity-specific connotations and the current cutoffs for obesity and overweight may not be useful indicators of clinical risk of obesity-related disorders, including NAFLD, in Asian populations. Asians, as compared to other ethnic groups, have been shown to have a higher prevalence of MS for similar grades of BMI, a disproportionate propensity to develop vascular disease and diabetes for any amount of weight gain at a given BMI, and a regional body fat partitioning that fosters more fat in visceral areas (visceral adipose tissue—VAT) as compared to total body adiposity, and as a result BMI may be a suboptimal measure for adiposity in Asians. The implication for NAFLD is that a person who is not overweight or centrally obese by the Western criteria, such as the Third National Health and Nutrition Examination Survey (NHANES III), might still have excessive amounts of adipose tissue (defined as >15 % of total tissue), particularly visceral adiposity. VAT has been shown to be biologically different as compared to subcutaneous adipose tissue in that it is more inflammatory and is associated with more aggressive MS-linked disease outcomes, including NAFLD and its vascular associations. This has prompted a revision of the BMI cutoffs for health risks for Asian populations with a lower value in each category (normal 18.5–22.9 and obesity >27.5 kg/m², instead of 30 in the Western populations) [92]. In addition, a waist circumference criteria (male >90 cm and female >80 cm) is widely used as useful anthropometric measures of central obesity in Asians. It has been shown that weight gain and increase in anthropometric indices of fatness, even while within the normal body weight and BMI range, might be producing fatty liver among Asians. Another aspect of this intriguing and complex relationship between body composition and NAFLD among Asians is the fact that ectopic fat depots might also contribute to the overall process of adiposity–MS–NAFLD–vascular disease relationship in Asians, and this needs to be looked into in larger focused studies [138, 143, 144].

**Insulin Resistance, Metabolic Syndrome, Diabetes, and Cardiovascular Disease in NAFLD [84, 89, 94, 97, 113, 114, 127]**

These conditions form a spectrum and insulin resistance (IR) holds key to the metabolic
syndrome (MS)-associated clinical outcomes. Varying degree of IR is present in two-thirds of NAFLD patients in Asia and in more than 95% of NASH subjects. The frequency and grade of IR increase with the severity of liver disease in NAFLD. IR is one of the factors associated with liver fibrosis progression in NASH, and histological improvements of NASH are associated with reciprocal changes in IR. Diabetes is the classical clinical expression of MS, and as such NAFLD is present in at least 50% of diabetes patients from Asia. Although this is similar to that observed in other populations, the frequency of diabetes at NAFLD diagnosis is lower in Asians (10–15%) as compared to others (25–40%). However, family history of diabetes is often present in NAFLD in Asia and the risk of development of diabetes is increased four- to fivefold within 4–6 years of NAFLD diagnosis. There is a linear relationship between the prevalence of components of MS and the risk of NAFLD in the population of Japan, China, Hong Kong, Korea, and India. Apart from diabetes, there seems to be a clearly demonstrable relationship between incident NAFLD and new development of hypertension in Asian population. Much of the increased cardiovascular risk in Asia occurs in the context of this shared relationship among MS clinical counterparts. NAFLD has been shown to be a good predictor of endothelial dysfunction and atherosclerotic vascular disease individually in different Asian populations, even in nondiabetic, non-hypertensive subjects. This expands the value of NAFLD detection as a general health risk in the population, beyond that posed through more traditional MS-linked associations in Asia.

**Diet and Physical Activity [144–148]**

NAFLD is an outcome of overnutrition and a result from an imbalance between intake of foods dense in calories and expenditure of energy through physical activity. The Asian countries are passing through a phase of differential but steadily progressive economic growth. This has an impact on the dietary habits and the social as well as cultural practices with increasing trend to adopt a Westernized lifestyle. Increasing urbanization and lesser dependence on jobs that necessitate physical labor along with increasing fat, protein, and calorie intake and availability of energy dense nutritionally imbalanced “fast” foods that have skewed nutritional values together with lesser intake of vegetables are factors that promote the nutritional–metabolic imbalance that culminates in MS and NAFLD. Among the nutritional components, cholesterol intake has been distinctly shown to be linked to NAFLD, while the role of fructose, complex carbohydrates, and micronutrients in Asian diet as contributors to NAFLD needs more focused studies. Further evidence for a role of diet and physical activity in NASH in Asian population has come from intervention studies. A Korean study undertook and evaluated the effects of exercise and diet modification on histological severity of steatosis in 120 living liver donors, only 59% of whom were overweight or obese. Lifestyle modification for 12 weeks achieved weight reduction in 77% of patients and steatosis improvement in 86%; reduction of serum total cholesterol >10% and weight >10% were strongly related to major improvements in steatosis.

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