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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].

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Table 2.1 Prevalence of NAFLD in the USA and Europe

Author, year	Country	Population	Sample size (<i>n</i>)	Prevalence of NAFLD (%)	Mode of diagnosis	Ref. No.
Price, 2014	USA	HIV+ and HIV– men in the Multicenter AIDS Cohort Study.	<i>N</i> = 719 <i>n</i> = 254 HIV-men <i>n</i> = 465 HIV + men	Overall-15 % HIV– = 19 % HIV+ = 13 %	Fatty liver was defined as a liver-to-spleen attenuation ratio < 1 on non-contrast computed tomography (CT).	[18]
World Gastroenterology Organization Global Guidelines, 2012	USA	A representative sample of the US population	NA	General population 27–34 % Morbid obesity 75–92 % European-Americans 33 % Hispanic Americans 45 % African Americans 24 %	A variety of sources not reported	[19]
Ruhl, 2003	USA	NHANES III (1988–1994)	5724	5.9 %	ALT > 43 U/L	[20]
Clark, 2003	USA	NHANES III (1988–1994)	15,676	10.3 %	ALT > 40 U/L and AST > 37 U/L for men and AST > 31 U/L for women	[21]
Browning, 2004	USA	Dallas Heart Study	734 (non Hispanic white only)	33 %	Hepatic triglyceride content > 5.5 %	[5]
Ioannou, 2006	USA	NHANES (1999–2002)	6823	9 %	ALT > 43 U/L or AST > 40 U/L	[22]
Lazo, 2013	USA	NHANES III (1988–1994)	12,454	19 %	Ultrasound	[23]
Schneider, 2014	USA	NHANES III (1988–1994)	4037	25.1 %	Ultrasound	[6]
Giday, 2006	USA	Local clinic data	320	19 %	Liver biopsies	[24]
Williams, 2011	USA	Cohort of middle age patients at large hospital	328	46 %	Ultrasound	[25]
Bedogni, 2005	Italy	Dionysos Project	3345	20 %	Ultrasound	[26]
Radu, 2008	Romania	Cohort of hospitalized patients	3005	20 %	Ultrasound	[27]
World Gastroenterology Organization Global Guidelines, 2012	Europe	A representative sample of the European population	NA	20–30 %	A variety of sources not reported	[1, 19]
Gastaldelli et al., 2009	14 EU countries	Healthy subjects between 30 and 60 years	1400	33 %	Fatty liver index	[28]
Haring, 2009	Germany	Subjects aged 20–79	4160	30.4 %	Ultrasound	[29]
Zois, 2010	Greece	Subjects aged 3–98 years old	498	31 %	Autopsy	[30]
Caballeria, 2010	Spain	Individuals aged 15–85 years old	773	33.4 %	Ultrasound	[31]

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, undiag-

nosed 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

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

US ultrasound, MRS magnetic resonance spectroscopy, CT computed tomography, NR not reported

^aUnadjusted prevalence

^bPrevalence of metabolic syndrome

^cNonobese defined as BMI <25 kg/m²

^dPrevalence of abnormal Fasting blood glucose

^eNonobese defined as BMI <23 kg/m² and waist circumference <80 cm (female)/<90 cm (male)

^fNonobese defined as BMI <23 kg/m²

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 2.3 Incidence of NAFLD in Asian countries

Author, year	Country	Population	Sample size (n)	Follow-up period	Incidence of NAFL	Mode of diagnosis	Risk factors for new NAFLD	Ref. no.
Wong et al., 2015	Hong Kong, China	General population (urban)	565	47 (34–60) months	78 (13.8 %); 13.5 % at 3–5 yr	MRS	Increase in WC and TG	[131]
Hamaguchi et al., 2005	Japan	Hospital health checkup	3147	414 ± 128 days	308 (10 %)	US	Presence of MS at baseline	[127]
Xu et al., 2013	China	Nonobese subjects ^a	5562	5 years	494 (8.8 %)	US	Age, gender, BMI, WC, TG, HDL, serum uric acid, Hb, and platelet count	[129]
Sung et al., 2014	South Korea	Hospital health checkup	11448	5 years (retrospective)	1418 (12.38 %)	US	Associated with new-onset hypertension	[130]
Donghee Kim et al., 2014	Korea	General population	1375	5 years	288 (20.9 %)	US	Increase in visceral adipose tissue	[132]
Pankaj Singh et al., 2014	West Bengal, India	Nonobese subjects in general population (rural) ^b	83	5 years	26 (31 %); 62.65 per 1000 person-year	US	Higher degree of adiposity at baseline and increase over time	[133]

US ultrasound, MRS magnetic resonance spectroscopy, WC waist circumference, TG triglyceride, BMI body mass index, Hb hemoglobin

^aNonobese defined as BMI <25 Kg/m²

^bNonobese 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.

References

1. Stephen E Roberts, David G Samuel, John G Williams, Kymberley Thorne, Sian Morrison-Rees, Ann John, Ashley Akbari, Judy C Williams. Survey of Digestive Health across Europe Part one: The burden of gastrointestinal diseases and the organization and delivery of gastroenterology services across Europe Report for United European Gastroenterology. August 2014. http://ueg.sagepub.com/content/suppl/2014/10/13/2050640614554154.DC1/Full_Survey.pdf
2. Brunello G, Michaud PC, Sanz-de-Galdeano A. The rise in obesity across the Atlantic: an Economic Perspective Preliminary version of a paper prepared for the 48th Panel Meeting of Economic Policy in Paris.
3. Venkatesan C, Younossi ZM. Potential mechanisms underlying the associations between liver enzymes and risk for type 2 diabetes. *Hepatology*. 2012;55(3):968–70. doi:10.1002/hep.24769.
4. Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol*. 2014;6(5):274–83. doi:10.4254/wjh.v6.i5.274.

5. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology*. 2004;40:1387–95. doi:10.1002/hep.20466 [PMID: 15565570].
6. Schneider AL, Lazo M, Selvin E, Clark JM. Racial differences in nonalcoholic fatty liver disease in the U.S. population. *Obesity* (Silver Spring). 2014;22:292–9.
7. Roberts KK, Cochet AE, Lamb PB, Brown PJ, Battafarano DF, Brunt EM, Harrison SA. The prevalence of NAFLD and NASH among patients with psoriasis in a tertiary care dermatology and rheumatology clinic. *Aliment Pharmacol Ther*. 2014;14(3):293–300. doi:10.1111/apt.13042.
8. Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther*. 2011;34(3):274–85. doi:10.1111/j.1365-2036.2011.04724.x.
9. Chalasani N, et al. The diagnosis and managements of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005–13.
10. Lazo M, Clark JM. The epidemiology of nonalcoholic fatty liver disease: a global perspective. *Semin Liver Dis*. 2008;28:339–50.
11. Loguercio C, De Girolamo V, de Sio I, Tuccillo C, Ascione A, Baldi F, Budillon G, Cimino L, Di Carlo A, Di Marino MP, Morisco F, Picciotto F, Terracciano L, Vecchione R, Verde V, Del Vecchio BC. Non-alcoholic fatty liver disease in an area of southern Italy: main clinical, histological, and pathophysiological aspects. *J Hepatol*. 2001;35(5):568–74. Erratum in: *J Hepatol* 2002 May;36(5):713.
12. Younossi ZM, Zheng L, Stepanova M, Henry L, Venkatesan C, Mishra A. Trends in Outpatient Resource Utilizations and Outcomes for Medicare Beneficiaries With Nonalcoholic Fatty Liver Disease. *J Clin Gastroenterol*. 2015;49(3):222–7.
13. Bedogni G, Miglioli L, Masutti F, Castiglione A, Croce LS, Tiribelli C, et al. Incidence and natural course of fatty liver in the general population: the Dionysos study. *Hepatology*. 2007;46:1387–91.
14. Musso G, Gambino R, Cassader M, Pagano G. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med*. 2011;43(8):617–49. doi:10.3109/07853890.2010.518623.
15. Haring R, Wallaschofski H, Nauck M, Dorr M, Baumeister SE, Volzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. *Hepatology*. 2009;50:1403–11.
16. Blachier M, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol*. 2013;58(3):593–608. doi:10.1016/j.jhep.2012.12.005.
17. Soresi M, Noto D, Cefalu AB, Martini S, Vigna GB, Fonda M, et al. Nonalcoholic fatty liver and metabolic syndrome in Italy: results from a multicentric study of the Italian Arteriosclerosis society. *Acta Diabetol*. 2013;50(2):241–9.
18. Price JC, Seaberg EC, Latanich R, Budoff MJ, Kingsley LA, Palella FR, et al. Risk factors for fatty liver in the multicenter AIDS cohort study. *Am J Gastroenterol*. 2014; 109:695–704; doi:10.1038/ajg.2014.32; published online 18 March 2014.
19. LaBrecque D, Abbas Z (Pakistan), Anania F, Ghafoor Khan A, Goh Malaysia K, et al. World Gastroenterology Organisation global guidelines. Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. June 2012. Available at: http://www.worldgastroenterology.org/assets/export/user-files/2012_NASH%20and%20NAFLD_Final_long.pdf. Last accessed on Aug 24, 2015
20. Ruhl CE, Everhart JE. Determinants of the association of overweight with elevated serum alanine aminotransferase activity in the United States. *Gastroenterology*. 2003;124:71–9.
21. Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. *Am J Gastroenterol*. 2003;98:960–7 [PMID: 12809815].
22. Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated serum alanine aminotransferase activity and calculated risk of coronary heart disease in the United States. *Hepatology*. 2006;43(5):1145–51.
23. Lazo M, Hernaez R, Eberhardt MS, Bonekamp S, Kamel I, Guallar E, Koteish A, Brancati FL, Clark JM. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. *Am J Epidemiol*. 2013;178:38–45.
24. Giday SA, Ashiny Z, Naab T, Smoot D, Banks A. Frequency of Nonalcoholic Fatty Liver Disease and Degree of Hepatic Steatosis in African-American Patients. *J Natl Med Assoc*. 2006;98(10):1613–5.
25. Williams CD, Stengel J, Asike MI, Torres DM, Shaw J, Contreras M, Landt CL, Harrison SA. Prevalence of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis among a largely middle-aged population utilizing ultrasound and liver biopsy: a prospective study. *Gastroenterology*. 2011;140(1):124–31.
26. Bedogni G, Miglioli L, Masutti F, Tiribelli C, Marchesini G, Bellentani S. Prevalence of and risk factors for nonalcoholic fatty liver disease: the Dionysos nutrition and liver study. *Hepatology*. 2005;42(1):44–52.
27. Radu C, Grigorescu M, Crisan D, Lupsor M, Constantin D, Dina L. Prevalence and associated

- risk factors of non-alcoholic fatty liver disease in hospitalized patients. *J Gastrointest Liver Dis*. 2008;17(3):255–60.
28. Gastaldelli A, Kozakova M, Hojlund K, Flyvbjerg A, Favuzzi A, Mitrakou A, et al. Fatty liver is associated with insulin resistance, risk of coronary heart disease, and early atherosclerosis in a large European population. *Hepatology*. 2009;49:1537–44.
29. Haring R, Wallaschofski H, Nauck M, Dorr M, Baumeister SE, Volzke H. Ultrasonographic hepatic steatosis increases prediction of mortality risk from elevated serum gamma-glutamyl transpeptidase levels. *Hepatology*. 2009;50:1403–11.
30. Zois CD, Baltayiannis GH, Bekiari A, Goussia A, Karayiannis P, Doukas M, et al. Steatosis and steatohepatitis in postmortem material from Northwestern Greece. *World J Gastroenterol*. 2010;16:3944–9.
31. Caballeria L, Pera G, Auladell MA, Toran P, Munoz L, Miranda D, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. *Eur J Gastroenterol Hepatol*. 2010;22:24–32.
32. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *J Am Med Assoc*. 2012;307(5):491–97. <http://jama.ama-assn.org/content/307/5/491>.
33. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999–2010. *J Am Med Assoc*. 2012;307(5):483–90. <http://jama.ama-assn.org/content/307/5/483>.
34. Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol*. 2008;49(4):608–12. doi:10.1016/j.jhep.2008.06.018.
35. Valantinas J, Apanaviciene DA, Maroziene L, Sveikata A. The prevalence of metabolic risk factors among outpatients with diagnosed nonalcoholic fatty liver disease in Lithuania. *Med Sci Monit*. 2012;18(5):PH57–62.
36. Hyysalo J, Männistö VT, Zhou Y, Arola J, Kärjä V, Leivonen M, Juuti A, Jaser N, Lallukka S, Käkälä P, Venesmaa S, Simonen M, Saltevo J, Moilanen L, Korpi-Hyövalti E, Keinänen-Kiukaanniemi S, Oksa H, Orho-Melander M, Valenti L, Fargion S, Pihlajamäki J, Peltonen M, Yki-Järvinen H. A population-based study on the prevalence of NASH using scores validated against liver histology. *J Hepatol*. 2014;60(4):839–46.
37. Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, Srishord M. Nonalcoholic fatty liver disease in lean individuals in the United States. *Medicine (Baltimore)*. 2012;91:319–27.
38. Hossain N, Afendy A, Stepanova M, Nader F, Srishord M, Rafiq N, Goodman Z, Younossi Z. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2009;7(11):1224.e1–9. doi:10.1016/j.cgh.2009.06.007.
39. Regimbeau JM, Colombat M, Mognol P, Durand F, Abdalla E, Degott C, et al. Obesity and diabetes as a risk factor for hepatocellular carcinoma. *Liver Transpl*. 2004;10:S69–73.
40. King LY, Khalili H, Chung H, Chan AT, Huang ES. Diabetes mellitus is associated with an increased risk of HCC in a large prospective cohort with long term follow-up. Presented at the American Association for the Study of Liver Disease (AASLD). Nov, 2014. Boston, MA.
41. Francque S, De Maeght S, Adler M, Deltenre P, de Galocsy C, Orlent H, VanSteenbergen W, Bastens B, Wain E, Langlet P, Lasser L, Verlinden W, Van Marck E, Henrion J; Steering Committee of the Belgian Association for the Study of the Liver. High prevalence of advanced fibrosis in association with the metabolic syndrome in a Belgian prospective cohort of NAFLD patients with elevated ALT. Results of the Belgian NAFLD registry. *Acta Gastroenterol Belg*. 2011;74(1):9–16.
42. Targher G, Bertolini L, Padovani R, Rodella S, Tessari R, Zenari L, et al. Prevalence of nonalcoholic fatty liver disease and its association with cardiovascular disease among type 2 diabetic patients. *Diabetes Care*. 2007;30:1212–8.
43. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. *Clin Gastroenterol Hepatol*. 2004;2(3):262–5. Erratum in: *Clin Gastroenterol Hepatol*. 2004 Jun;2(6):522.
44. Rafiq N, Bai C, Fang Y, Srishord M, McCullough A, Gramlich T, Younossi ZM. Long-term follow-up of patients with nonalcoholic fatty liver. *Clin Gastroenterol Hepatol*. 2009;7(2):234–8. doi:10.1016/j.cgh.2008.11.005.
45. Baranova A, Tran TP, Bireddine A, Younossi ZM. Systematic review: association of polycystic ovary syndrome with metabolic syndrome and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2011;33(7):801–14. doi:10.1111/j.1365-2036.2011.04579.x.
46. Baranova A, Tran TP, Afendy A, Wang L, Shamsaddini A, Mehta R, Chandhoke V, Bireddine A, Younossi ZM. Molecular signature of adipose tissue in patients with both non-alcoholic fatty liver disease (NAFLD) and polycystic ovarian syndrome (PCOS). *J Transl Med*. 2013;11:133. doi:10.1186/1479-5876-11-133.
47. Welzel TM, Graubard BI, Zeuzem S, El-Serag HB, Davila JA, McGlynn KA. Metabolic syndrome increases the risk of primary liver cancer in the United States: a study in the SEER-Medicare database. *Hepatology*. 2011;54:463–71. doi:10.1002/hep.24397 [PMID: 21538440].
48. Moore JB. Non-alcoholic fatty liver disease: the hepatic consequence of obesity and the metabolic syndrome. *Proc Nutr Soc*. 2010;69(2):211–20. doi:10.1017/S0029665110000030.
49. Zeb I, Katz R, Nasir K, Ding J, Rezaeian P, Budoff MJ. Relation of nonalcoholic fatty liver disease to

- the metabolic syndrome: the Multi-Ethnic Study of Atherosclerosis. *J Cardiovasc Comput Tomogr*. 2013;7(5):311–8. doi:10.1016/j.jcct.2013.08.011.
50. Smits MM, Ioannou GN, Boyko EJ, Utzschneider KM. Nonalcoholic fatty liver disease as an independent manifestation of the metabolic syndrome: results of a US national survey in three ethnic groups. *J Gastroenterol Hepatol*. 2013;28:664–70.
 51. Liangpunsakul S, Chalasani N. Unexplained elevations in alanine aminotransferase in individuals with the metabolic syndrome: results from the third National Health and Nutrition Survey (NHANES III). *Am J Med Sci*. 2005;329:111–6.
 52. Kim D, Chung G, Kwak M. Body fat distribution and the risk of incident and remittent nonalcoholic fatty liver disease: Prospective Cohort Study. Presented at the American Association for the Study of Liver Disease (AASLD). Nov, 2014. Boston, MA.
 53. Matteoni CA, Younossi ZM, Gramlich T, et al. Nonalcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology*. 1999;116(6):1413–9.
 54. Rosmorduc O, Fartoux L. HCC and NASH: how strong is the clinical demonstration? *Clin Res Hepatol Gastroenterol*. 2012;36:202–8. doi:10.1016/j.clinre.2011.12.011 [PMID: 22326764].
 55. Borena W, Strohmaier S, Lukanova A, Bjørge T, Lindkvist B, Hallmans G, Edlinger M, Stocks T, Nagel G, Manjer J, Engeland A, Selmer R, Häggström C, Tretli S, Concini H, Jonsson H, Stattin P, Ulmer H. Metabolic risk factors and primary liver cancer in a prospective study of 578,700 adults. *Int J Cancer*. 2012;131:193–200. doi:10.1002/ijc.26338 [PMID: 21805476].
 56. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology*. 2011;141:1249–53. doi:10.1053/j.gastro.2011.06.061 [PMID: 21726509].
 57. Karlas T, Wiegand J, Berg T. Gastrointestinal complications of obesity: non-alcoholic fatty liver disease (NAFLD) and its sequelae. *Best Pract Res Clin Endocrinol Metab*. 2013;27(2):195–208. doi:10.1016/j.beem.2013.02.002.
 58. Yilmaz Y. Review article: non-alcoholic fatty liver disease and osteoporosis-clinical and molecular crosstalk. *Aliment Pharmacol Ther*. 2012;36:345–52.
 59. Sanyal AJ, Banas C, Sargeant C, Luketic VA, Sterling RK, Stravitz RT, et al. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology*. 2006;43:682–9.
 60. Ascha MS, Hanounieh IA, Lopez R, Tamimi TA, Feldstein AF, Zein NN. The incidence and risk factors of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis. *Hepatology*. 2010;51:1972–8.
 61. Yasui K, Hashimoto E, Komorizono Y, Koike K, Arii S, Imai Y, et al. Characteristics of patients with nonalcoholic steatohepatitis who develop hepatocellular carcinoma. *Clin Gastroenterol Hepatol*. 2011;9:428–33.
 62. Baffy G, Brunt E, Caldwell S. Hepatocellular carcinoma in non-alcoholic fatty liver disease: an emerging menace. *J Hepatol*. 2012;56:1384–91.
 63. Zazos P, Renner EL. Liver transplantation and non-alcoholic fatty liver disease. *World J Gastroenterol*. 2014;20(42):15532–8.
 64. Ratziu V, Bellentani S, Cortez-Pinto H, et al. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol*. 2010;53(2):372–84.
 65. Brunt EM, Kleiner DE, Wilson LA, Belt P, Neuschwander-Tetri BA. NASH Clinical Research Network (CRN). Nonalcoholic fatty liver disease (NAFLD) activity score and the histopathologic diagnosis in NAFLD: distinct clinicopathologic meanings. *Hepatology*. 2011;53(3):810–20. doi:10.1002/hep.24127.
 66. Otgonsuren M, Stepanova M, Gerber L, Younossi ZM. Anthropometric and clinical factors associated with mortality in subjects with nonalcoholic fatty liver disease. *Dig Dis Sci*. 2013;58(4):1132–40. doi:10.1007/s10620-012-2446-3.
 67. NAFLD and the FLIP consortia. Available from the world wide web at: http://www.easl.eu/_newsroom/latest-news/nafl-and-the-the-flip-consortia. Last accessed on 12 Jan 2015.
 68. Leslie T, Pawloski L, Kallman-Price J, Escheik C, Hossain N, Fang Y, Gerber LH, Younossi ZM. Survey of health status, nutrition and geography of food selection of chronic liver disease patients. *Ann Hepatol*. 2014;13(5):533–40.
 69. Puig J, Blasco G, Daunis-I-Estadella J, Loshuertos E, Codina J, Cuba V, Ortiz R, Xifra G, Ricart W, Pedraza S, Federici M, Fernández-Real JM. Nonalcoholic fatty liver disease and age are strong indicators for atherosclerosis in morbid obesity. *Clin Endocrinol (Oxf)*. 2014. doi:10.1111/cen.12698.
 70. Suomela E, Oikonen M, Virtanen J, Parkkola R, Jokinen E, Laitinen T, Hutri-Kähönen N, Kähönen M, Lehtimäki T, Taittonen L, Tossavainen P, Jula A, Loo BM, Mikkilä V, Younossi Z, Viikari JS, Juonala M, Raitakari OT. Prevalence and determinants of fatty liver in normal-weight and overweight young adults. The Cardiovascular Risk in Young Finns Study. *Ann Med*. 2014;21:1–7.
 71. Biredinc A, Stepanova M, Pawloski L, Younossi ZM. Caffeine is protective in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2012;35(1):76–82. doi:10.1111/j.1365-2036.2011.04916.x.
 72. Stepanova M, Younossi ZM. Independent association between nonalcoholic fatty liver disease and cardiovascular disease in the US population. *Clin Gastroenterol Hepatol*. 2012;10(6):646–50. doi:10.1016/j.cgh.2011.12.039.
 73. Sharma H, Estep M, Biredinc A, Afendy A, Moazzez A, Elariny H, Goodman Z, Chandhoke V, Baranova

- A, Younossi ZM. Expression of genes for microRNA-processing enzymes is altered in advanced non-alcoholic fatty liver disease. *J Gastroenterol Hepatol*. 2013;28(8):1410–5. doi:10.1111/jgh.1226.
74. Kim Y, Surabattula R, Park K, Weng S, Schuppan D. A diet-induced mouse model with development of severe Nash. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
75. Ganz M, Csak T, Bala S, Saha B, Szabo G. NAFLD progression to NASH is associated with cumulative danger signals, M1 macrophage phenotype and increased microRNA-155 expression that contributes to fibrosis in a high fat/cholesterol/sugar diet feeding in mice. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
76. Asgharpour A, Pacana T, Vincent R, Cazanave SC, Mirshahi F, Seneshaw M, Daita K, Puri P, Sanyal AJ. Characterization of a diet-induced mouse model of nonalcoholic fatty liver disease with reproducible progression to advanced fibrosis and hepatocellular carcinoma. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
77. Nishida N, Yada N, Chishina H, Arizumi T, Takita M, Kitai S, Inoue T, Hagiwara S, Minami Y, Ueshima K, Sakurai T, Kudo M. Pathological feature, oxidative DNA damage and epigenetic alteration of tumor suppressor genes in nonalcoholic fatty liver disease. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
78. Nishikawa T, Yasui K, Yamaguchi K, Moriguchi M, Sumida Y, Mitsuyoshi H, Minami M, Itoh Y. Impaired metabolic compensation in adipose tissues and functional alignment by complemented stem cells in mice with progressive nonalcoholic fatty liver disease. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
79. Ruiz A, Cabrera D, Quintero P, Pizarro M, Solis N, Barrera F, Arrese M. Diet-induced nonalcoholic fatty liver disease is associated with sarcopenia and decreased serum insulin growth factor-1. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
80. Hur W, Kim J, Lee J, Hong S, Yoon S. miR-451 inhibits palmitic acid-induced proinflammatory cytokine IL-8 expression through AMPK/AKT pathway in non-alcoholic steatohepatitis. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
81. Kessoku T, Honda Y, Ogawa Y, Tomeno W, Imajo K, Mawatari H, Saito S, Nakajima A. Mechanism analysis of microRNA-27b causing the fatty liver formation and insulin resistance at the same onset. Presented at the American Association for the Study of Liver Disease (AASLD), Nov 2014. Boston, MA.
82. Gerber L, Otgonsuren M, Mishra A, Escheik C, Bireddine A, Stepanova M, Younossi ZM. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. *Aliment Pharmacol Ther*. 2012;36(8):772–81. doi:10.1111/apt.12038.
83. Sanyal AJ. NASH: a global health problem. *Hepatol Res*. 2011;41(7):670–4.
84. Farrell GC, Wong VW, Chitturi S. NAFLD in Asia—as common and important as in the West. *Nat Rev Gastroenterol Hepatol*. 2013;10(5):307–18.
85. Amarapurkar DN, Hashimoto E, Lesmana LA, Sollano JD, Chen PJ, Goh KL. Asia-Pacific Working Party on NAFLD. How common is non-alcoholic fatty liver disease in the Asia-Pacific region and are there local differences? *J Gastroenterol Hepatol*. 2007;22(6):788–93.
86. Beaglehole R, Bonita R, Horton R, Adams C, Alleyne G, Asaria P et al; Lancet NCD Action Group; NCD Alliance. Priority actions for the non-communicable disease crisis. *Lancet*. 2011;377(9775):1438–47.
87. Finucane MM, Stevens GA, Cowan MJ, Danaei G, Lin JK, Paciorek CJ et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. *Lancet*. 2011;377(9765):557–67.
88. Deurenberg P, Yap M, van Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. *Int J Obes Relat Metab Disord*. 1998;22(12):1164–71.
89. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Bugianesi E, Lenzi M, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes*. 2001;50(8):1844–50.
90. Palaniappan LP, Wong EC, Shin JJ, Fortmann SP, Lauderdale DS. Asian Americans have greater prevalence of metabolic syndrome despite lower body mass index. *Int J Obes (Lond)*. 2011;35(3):393–400.
91. Petersen KF, Dufour S, Feng J, Befroy D, Dziura J, Dalla Man C, Cobelli C, Shulman GI. Increased prevalence of insulin resistance and nonalcoholic fatty liver disease in Asian-Indian men. *Proc Natl Acad Sci USA*. 2006;103(48):18273–7.
92. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004;363(9403):157–63.
93. Chitturi S, Farrell GC, Hashimoto E, Saibara T, Lau GK, Sollano JD, Asia-Pacific Working Party on NAFLD. Non-alcoholic fatty liver disease in the Asia-Pacific region: definitions and overview of proposed guidelines. *J Gastroenterol Hepatol*. 2007;22(6):778–87.

94. Wong RJ, Ahmed A. Obesity and non-alcoholic fatty liver disease: disparate associations among Asian populations. *World J Hepatol.* 2014;6(5):263–73.
95. Wang FS, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. *Hepatology.* 2014;60(6):2099–108.
96. Rehm J, Samokhvalov AV, Shield KD. Global burden of alcoholic liver diseases. *J Hepatol.* 2013; 59(1):160–8.
97. Wong GL, Wong VW, Choi PC, Chan AW, Chim AM, Yiu KK, Chan HY, Chan FK, Sung JJ, Chan HL. Metabolic syndrome increases the risk of liver cirrhosis in chronic hepatitis B. *Gut.* 2009;58(1):111–7.
98. Fan JG, Zhu J, Li XJ, Chen L, Li L, Dai F, Li F, Chen SY. Prevalence of and risk factors for fatty liver in a general population of Shanghai. *China J Hepatol.* 2005;43(3):508–14.
99. Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. *Gut.* 2012;61(3):409–15.
100. Chen CH, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, Yueh SK. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. *J Clin Gastroenterol.* 2006;40(8):745–52.
101. Park SH, Jeon WK, Kim SH, Kim HJ, Park DI, Cho YK, 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.
102. Omagari K, Kadokawa Y, Masuda J, Egawa I, Sawa T, Hazama H, et al. Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J Gastroenterol Hepatol.* 2002; 17(10):1098–105.
103. Jimba S, Nakagami T, Takahashi M, Wakamatsu T, Hirota Y, Iwamoto Y, Wasada T. Prevalence of non-alcoholic fatty liver disease and its association with impaired glucose metabolism in Japanese adults. *Diabet Med.* 2005;22(9):1141–5.
104. Amarapurkar D, Kamani P, Patel N, Gupte P, Kumar P, Agal S, et al. Prevalence of non-alcoholic fatty liver disease: population based study. *Ann Hepatol.* 2007;6(3):161–3.
105. Das K, Das K, Mukherjee PS, Ghosh A, Ghosh S, Mridha AR, et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. *Hepatology.* 2010;51(5):1593–602.
106. Vendhan R, Amutha A, Anjana RM, Unnikrishnan R, Deepa M, Mohan V. Comparison of characteristics between nonobese and overweight/obese subjects with nonalcoholic fatty liver disease in a South Indian population. *Diabetes Technol Ther.* 2014; 16(1):48–55.
107. Dassanayake AS, Kasturiratne A, Rajindrajith S, Kalubowila U, Chakrawarthi S, De Silva AP, et al. Prevalence and risk factors for non-alcoholic fatty liver disease among adults in an urban Sri Lankan population. *J Gastroenterol Hepatol.* 2009;24(7): 1284–8.
108. Niaz A, Ali Z, Nayyar S, Fatima N. Prevalence of NAFLD in Healthy and Young Male Individuals. *ISRNGastroenterol.* 2011;2011:363546.
109. Wong VW. Nonalcoholic fatty liver disease in Asia: a story of growth. *J Gastroenterol Hepatol.* 2013; 28(1):18–23.
110. Mohan V, Farooq S, Deepa M, Ravikumar R, Pitchumoni CS. Prevalence of non-alcoholic fatty liver disease in urban south Indians in relation to different grades of glucose intolerance and metabolic syndrome. *Diabetes Res Clin Pract.* 2009;84(1): 84–91.
111. Fan JG, Farrell GC. Epidemiology of non-alcoholic fatty liver disease in China. *J Hepatol.* 2009;50(1): 204–10.
112. Hou XH, Zhu YX, Lu HJ, Chen HF, Li Q, Jiang S, Xiang KS, Jia WP. Non-alcoholic fatty liver disease's prevalence and impact on alanine aminotransferase associated with metabolic syndrome in the Chinese. *J Gastroenterol Hepatol.* 2011;26(4): 722–30.
113. Yan J, Xie W, Ou WN, Zhao H, Wang SY, Wang JH, et al. Epidemiological survey and risk factor analysis of fatty liver disease of adult residents, Beijing. *China J Gastroenterol Hepatol.* 2013;28(10):1654–9.
114. Chen CH, Huang MH, Yang JC, Nien CK, Yang CC, Yeh YH, Yueh SK. Prevalence and etiology of elevated serum alanine aminotransferase level in an adult population in Taiwan. *J Gastroenterol Hepatol.* 2007;22(9):1482–9.
115. Tsai CH, Li TC, Lin CC. Metabolic syndrome as a risk factor for nonalcoholic fatty liver disease. *South Med J.* 2008;101(9):900–5.
116. Okanoue T, Umemura A, Yasui K, Itoh Y. Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis in Japan. *J Gastroenterol Hepatol.* 2011;26 Suppl 1:153–62.
117. Matsuura B, Nunoi H, Miyake T, Hiasa Y, Onji M. Obesity and gastrointestinal liver disorders in Japan. *J Gastroenterol Hepatol.* 2013;28 Suppl 4:48–53.
118. Fan JG, Li F, Cai XB, Peng YD, Ao QH, Gao Y. The importance of metabolic factors for the increasing prevalence of fatty liver in Shanghai factory workers. *J Gastroenterol Hepatol.* 2007;22(5): 663–8.
119. Wang Z, Xia B, Ma C, Hu Z, Chen X, Cao P. Prevalence and risk factors of fatty liver disease in the Shuiguohu district of Wuhan city, central China. *Postgrad Med J.* 2007;83(977):192–5.
120. Pinidiyapathirage MJ, Dassanayake AS, Rajindrajith S, Kalubowila U, Kato N, Wickremasinghe AR, de Silva HJ. Non-alcoholic fatty liver disease in a rural, physically active, low income population in Sri Lanka. *BMC Res Notes.* 2011;4:513.
121. Malik A, Cheah PL, Hilmi IN, Chan SP, Goh KL. Non-alcoholic fatty liver disease in Malaysia: a

- demographic, anthropometric, metabolic and histological study. *J Dig Dis*. 2007;8(1):58–64.
122. Duseja A, Chalasani N. Epidemiology and risk factors of nonalcoholic fatty liver disease (NAFLD). *Hepatol Int*. 2013;7(2 Suppl):755–64.
 123. Fan JG. Epidemiology of alcoholic and nonalcoholic fatty liver disease in China. *J Gastroenterol Hepatol*. 2013;28 Suppl 1:11–7.
 124. Das K, Chowdhury A. Lean NASH: distinctiveness and clinical implication. *Hepatol International*. 2013;7(2 Suppl):806–13.
 125. Kim HJ, Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, et al. Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. *Arch Intern Med*. 2004;164(19):2169–75.
 126. Ruderman NB, Schneider SH, Berchtold P. The “metabolically-obese,” normal-weight individual. *Am J Clin Nutr*. 1981;34(8):1617–21.
 127. Hamaguchi M, Kojima T, Takeda N, Nakagawa T, Taniguchi H, Fujii K, et al. The metabolic syndrome as a predictor of nonalcoholic fatty liver disease. *Ann Intern Med*. 2005;143(10):722–8.
 128. Zelber-Sagi S, Lotan R, Shlomai A, Webb M, Harrari G, Buch A, et al. Predictors for incidence and remission of NAFLD in the general population during a seven-year prospective follow-up. *J Hepatol*. 2012;56(5):1145–51.
 129. Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: the Zhejiang Zhenhai Study. *Am J Gastroenterol*. 2013;108(8):1299–304.
 130. Sung KC, Wild SH, Byrne CD. Development of new fatty liver, or resolution of existing fatty liver, over five years of follow-up, and risk of incident hypertension. *J Hepatol*. 2014;60(5):1040–5.
 131. Wong VW, Wong GL, Yeung DK, Lau TK, Chan CK, Chim AM, et al. Incidence of non-alcoholic fatty liver disease in Hong Kong: A population study with paired proton-magnetic resonance spectroscopy. *J Hepatol*. 2015;62(1):182–9.
 132. Kim D, Chung GE, Kwak M-S, Kim W, Kim YJ, Yoon J-H. Body fat distribution and the risk of incident and remittent nonalcoholic fatty liver disease: Prospective Cohort Study. *Hepatology*. 2014; 60 (4) (Suppl S1):599A (Abstract No. 828).
 133. Singh P, Das K, Misra D, Ray G, Santra A, Chowdhury A. Dynamicity of adiposity determine evolution of non-alcoholic fatty liver even in lean subjects: a prospective cohort study. *Hepatology*. 2014; 60(4) (Suppl S1):600A (Abstract No. 829)
 134. Loomba R, Sirlin CB, Schwimmer JB, Lavine JE. Advances in pediatric nonalcoholic fatty liver disease. *Hepatology*. 2009;50(4):1282–93.
 135. Alkassabany YM, Farghaly AG, El-Ghitany EM. Prevalence, risk factors, and predictors of non-alcoholic fatty liver disease among schoolchildren: a hospital-based study in Alexandria, Egypt. *Arab J Gastroenterol*. 2014;15(2):76–81.
 136. Alavian SM, Mohammad-Alizadeh AH, Esna-Ashari F, Ardalan G, Hajarizadeh B. Non-alcoholic fatty liver disease prevalence among school-aged children and adolescents in Iran and its association with biochemical and anthropometric measures. *Liver Int*. 2009;29(2):159–63.
 137. Lee YS, Kek BL, Poh LK, Saw SM, Loke KY. Association of raised liver transaminases with physical inactivity, increased waist-hip ratio, and other metabolic morbidities in severely obese children. *J Pediatr Gastroenterol Nutr*. 2008;47(2):172–8.
 138. Liu CJ. Prevalence and risk factors for NAFLD in Asian people who are not obese. *J Gastroenterol Hepatol*. 2012;27(10):1555–60.
 139. Chang Y, Ryu S, Sung E, Woo HY, Cho SI, Yoo SH, et al. Weight gain within the normal weight range predicts ultrasonographically detected fatty liver in healthy Korean men. *Gut*. 2009;58(10):1419–25.
 140. Rahman M, Temple JR, Breitkopf CR, Berenson AB, et al. Racial differences in body fat distribution among reproductive-aged women. *Metabolism*. 2009;58(9):1329–37.
 141. Du T, Sun X, Yin P, Huo R, Ni C, Yu X. Increasing trends in central obesity among Chinese adults with normal body mass index, 1993-2009. *BMC Public Health*. 2013;13:327.
 142. Paredes AH, Serfaty L, Oliveira CP, Chowdhury A, Boyett SL, Siddiqui MS, Sanyal AJ. There is substantial phenotypic variability in lean versus obese subjects with NAFLD across the world: The Global NASH Study. *Hepatology*. 2014; 60(4) (Suppl S1):593A (Abstract No. 815).
 143. Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJ, Chutaputti A. Asia-Pacific Working Party for NAFLD. What are the risk factors for non-alcoholic fatty liver disease in Asia-Pacific? *J Gastroenterol Hepatol*. 2007;22(6):794–800.
 144. Kim NH, Park J, Kim SH, Kim YH, Kim DH, Cho GY, et al. Non-alcoholic fatty liver disease, metabolic syndrome and subclinical cardiovascular changes in the general population. *Heart*. 2014;100(12):938–43.
 145. Toshimitsu K, Matsuura B, Ohkubo I, Niiya T, Furukawa S, Hiasa Y, et al. Dietary habits and nutrient intake in non-alcoholic steatohepatitis. *Nutrition*. 2007;23(1):46–52.
 146. Enjoji M, Nakamura M. Is the control of dietary cholesterol intake sufficiently effective to ameliorate non-alcoholic fatty liver disease? *World J Gastroenterol*. 2010;16(7):800–3.
 147. Magosso E, Ansari MA, Gopalan Y, Abu Bakar MR, Karim Khan NA, Wong JW, et al. Prevalence of non-alcoholic fatty liver in a hypercholesterolemic population of northwestern peninsula Malaysia. *Southeast Asian J Trop Med Public Health*. 2010;41(4):936–42.
 148. Jin YJ, Kim KM, Hwang S, Lee SG, Ha TY, Song GW, et al. Exercise and diet modification in

- non-obese non-alcoholic fatty liver disease: analysis of biopsies of living liver donors. *J Gastroenterol Hepatol*. 2012;27(8):1341–7.
149. Wong VW, Wong GL, Choi PC, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut*. 2010;59(7):969–74.
 150. Argo CK, Caldwell SH. Epidemiology and natural history of non-alcoholic steatohepatitis. *Clin Liver Dis*. 2009;13(4):11–531.
 151. Caldwell S, Argo C. The natural history of non-alcoholic fatty liver disease. *Dig Dis*. 2010;28:162–8.
 152. Adams LA, Lymp JF, St Sauver J, Sanderson SO, Lindor KD, Feldstein A, Angulo P. The natural history of nonalcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113–21. [PMID: 16012941] (hazard ratio for mortality).
 153. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011–2012. *JAMA*. 2014;311(8):806–14. doi:10.1001/jama.2014.732.
 154. Paredes AH, et al. Nonalcoholic fatty liver disease. *Clin Liver Dis*. 2012;16:397–419.
 155. European Union Commission Final Report Summary - FLIP (Fatty liver: Inhibition of Progression). Last updated on 2014-08-29. Retrieved on 2015-01-01 at Permalink: http://cordis.europa.eu/result/rcn/147495_en.html

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