Original Article

The Risk Factors for Ultrasound-diagnosed Non-alcoholic Fatty Liver Disease Among Adolescents

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) is garnering increasing interest and acceptance as one of the most important causes of chronic liver disease. The aim of this study was to investigate the risk factors for NAFLD among selected adolescent students in Hualien City, Taiwan. Materials and Methods: A stratified random sampling scheme was carried out among 1724 adolescent students aged 12 or 13 years old in Hualien City. In total, 220 students (normal: overweight: obese = 97:48:75) agreed to join the study. They underwent physical examination, laboratory tests and ultrasonography examination of the liver. Diagnosis of NAFLD in this study was based on sonographic evidence of a fatty liver and testing negative for serum HBsAg and anti-HCV antibody. Results: Of the 220 participants, 4 were excluded because they tested positive for HBsAg or anti-HCV antibody. NAFLD was detected in 86 (39.8%) out of the 216 subjects. The rate of NAFLD in the adolescents increased progressively from 16.0% in the normal group to 50.5% in the overweight group, and 63.5% among the obese subjects. Compared to their normal counterparts, adolescents with NAFLD had a significantly higher weight, body mass index (BMI), waist circumference, levels of alanine aminotransferase (ALT), triglyceride and non-high-density-lipoprotein (non-HDL) cholesterol. However, among the participants with NAFLD, only 20 (23.3%) showed ALT abnormality but there was an increasing trend of ALT abnormality as the severity of fatty liver increased. In addition, the higher ALT, Homeostasis model assessment- insulin resistance (HOMA-IR), cholesterol, triglyceride, and non-HDL levels and lower HDL-C as the severity of fatty liver increased. In a stepwise logistic regression analysis, the most significant factor associated with the presence of NAFLD was weight category. When compared with their normal counterparts, overweight and obese adolescents had a 4.14 and 5.98 times the risk of having NAFLD, respectively. Elevated ALT was the second most important factor as adolescents with elevated ALT were more likely to have NAFLD (odds ratio = 3.32, 95% CI: 1.16 to 9.50). Non-HDL cholesterol level was the third most important factor associated with NAFLD with a 3.81-fold increase in risk incurred for every l n (1 mg/dL) increment. Conclusions: Obesity, ALT abnormality and elevated non-HDL-cholesterol are risk factors for NAFLD in adolescents. However, only 23.3% of the adolescents with NAFLD showed an abnormality for ALT. Therefore, ALT alone is not a sufficient indicator; and it is recommended that ultrasonography of the liver should be part of the routine health examination of obese adolescents.

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Key words: Adolescents, Non-alcoholic fatty liver disease, Obese, Risk factors

Introduction

Non-alcoholic fatty liver disease (NAFLD) is increasing recognised as one of the most important causes of chronic liver disease in Western countries.[1] It encompasses a spectrum of diseases ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH). Hepatic steatosis is a common clinical and histological finding and it is considered a benign condition, whereas NASH is an aggressive liver disease that leads to advanced fibrosis, cirrhosis and even hepatic failure.[1-3] The prevalence of NAFLD in adults is about 20% (range, 15 to 39) and the prevalence of NASH is 2% to 3% (range, 1.2 to 4.8).[4] Although the real mechanism behind hepatic steatosis is still elusive, it can occur in association with obesity, type 2 diabetes mellitus, drug-induced or viral hepatitis, hyperuricaemia, hyperlipidaemia and other

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conditions.[2-3, 5-11] Attention paid to NAFLD and its related risk factors has shifted from adults to young adolescents in recent years [7, 12-14] and it can be foreseen that the prevalence of NAFLD will become increasingly important as the global epidemic of childhood obesity rises. In Taiwan, a few adult studies have been done and these have revealed that the related risk factors for fatty liver include obesity, hyperglycaemia, hyperuricaemia and hypertriglycaemia.[10,11] The primary purpose of this community-based study was to investigate the risk factors for NAFLD among selected adolescent students in Taiwan.

Materials and Methods

The obesity survey was performed among all first-year junior high school students, aged 12 or 13 years old, in Hualien City, Taiwan, in 2002.[15] There were in total 1826 registered students, of whom 52 were not within the desired age and an additional 40 failed to attend, thus, leaning1724 adolescents as shown in Figure 1. The age-sex specific cut-off values of 85th and 95th percentiles of body mass index (BMI) from a nation-wide study were used to define overweight and obese children.[16] These values are also the nation-wide standard of the Department of Health Bureau of Taiwan.[17] The survey of the 1724 adolescents revealed that the number (rate) of normal, overweight and obese adolescents were 1233 (71.5%), 225 (13.1%), and 266 (15.4%), respectively.[15]

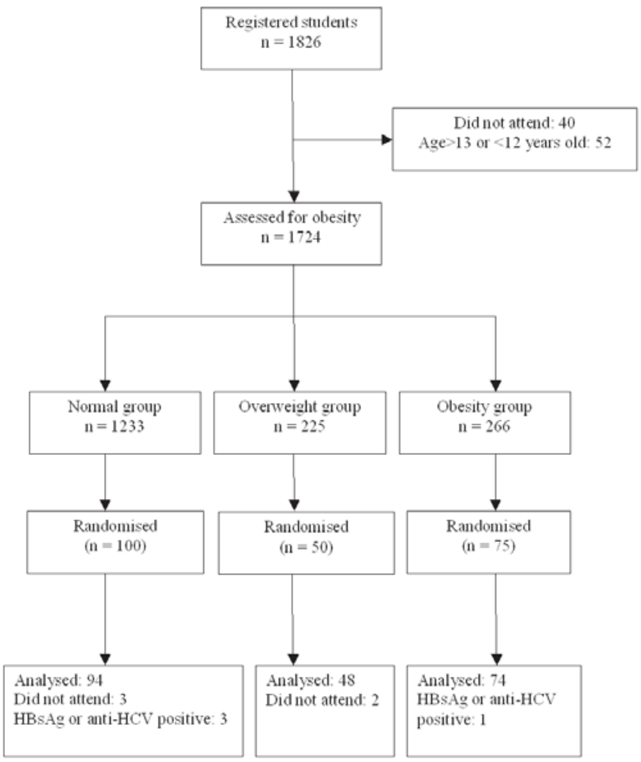

Fig.1. Flow chart depicting the study.

Under constraint of the research budget, it was not feasible to examine all children or use simple random sampling method to recruit enough study subjects with fatty liver. Therefore, a stratified random sampling method was applied, first grouping the total research population into three groups of normal, overweight and obese. Then 100 subjects are randomly selected from the normal group, 50 from the overweight group. As the obese group had more subjects than the overweight group, 75 of them were selected with random sampling as shown in Figure 1. Five of the selected recruits refused to be included in the study because their parents believed they are in good health and that there was no need for them to have the examination and blood check-up. In summary, 220 students (normal: overweight: obese = 97:48:75) agreed to participate in this study. Data regarding the current body height, body weight, together with the waist circu mferences of the patients were collected. Weight was measured in light clothing, while height was measured to the nearest 0.1 cm with the head held in the Frankfort plane. Waist circumference was taken midway between the inferior margin of the last rib and the crest of the iliac bone in a horizontal plane and measured to the nearest 0.1cm. After an overnight fast, serum total cholesterol, triglycerides, high-density-lipoprotein (HDL) cholesterol, alanine aminotransferase (ALT), fasting plasma sugar, plasma insulin, hepatitis B surface antigen (HBsAg) and anti-hepatitis C virus antibody (anti-HCV) were measured in all participants. Fasting plasma insulin concentrations, HBsAg and anti-HCV were measured by microparticle enzyme immunoassay (Axsym Insulin Reagent Pack, Abbott Laboratories, Abbott Park, IL, USA). Total cholesterol, triglyceride, HDL cholesterol and ALT concentration were measured by an enzymatic colorimetric method using a Hitachi 717 automated analyser (Hitachi Corp, Tokyo, Japan). Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol using the Friedewald equation[18] and none of our study subjects had a triglyceride level >400 mg/dL. Homeostasis model assessment- insulin resistance (HOMA-IR) was used to evaluate insulin sensitivity.

Ultrasonographic examination of liver and gallbladder was performed by an experienced hepatologist, who was unaware of both the aims of the study and the participants' biochemical profiles. An ultrasound device with a 3.5 MHz convex-type transducer (GE LOGIQ α 100MP, GE Medical Systems, Milwaukee, Wisconsin, USA) was used. Fatty liver was diagnosed based on the ultrasonographic pattern and graded as absent, mild, moderate and severe according to the criteria described by Needleman et al.[19] Diagnosis of NAFLD in this study was based on sonographic evidence of a fatty liver and a negative test result for HBsAg and anti-HCV antibody. None of the participants had a history of alcohol consumption and liver disease, hypertension or diabetes.

Table 1. Basic Characteristics of the Study Groups

Variables	Males (n = 134)	Females (n = 82)	*P* value*
Number (%)			
Normal	55 (41.0%)	39 (47.6%)	
Overweight	24 (17.9%)	24 (29.2%)	
Obese	55 (41.0%)	19 (23.2%)	0.01
Means ± standard deviation			
Age (y)	12.5 ± 0.5	12.5 ± 0.5	>0.05
BMI (kg/m^2)	25.5 ± 5.6	23.4 ± 4.6	0.004
Waist (cm)	83.1 ± 13.7	74.9 ± 11.7	<0.001
HOMA-IR	1.4 ± 1.9	1.3 ± 1.0	>0.05
Cholesterol (mg/dL)	151 ± 26	162 ± 31	0.006
Triglyceride (mg/dL)	90 ± 53	80 ± 36	>0.05
HDL-C (mg/dL)	56 ± 12	61 ± 12	0.01
Non-HDL-C (mg/dL)	95 ± 26	101 ± 28	>0.05
ALT (IU/L)	24.5 ± 24.0	17.5 ± 17.9	0.02

ALT: alanine aminotransferase; HDL-C: high-density-lipoprotein cholesterol; HOMA: homeostasis model assessment; Non-HDL-C: non-high-density-lipoprotein cholesterol;

* *P* value by chi-square test, unpaired Student's *t*-test or Mann-Whitney U test

The investigation was approved by the Ethics Committee of the Buddhist Tzu Chi General Hospital (Hualien, Taiwan). The details of this study were carefully explained to participants and their parents, and written informed consent was obtained.

Data were analysed using the SPSS PC software package. Unpaired Student's *t*-test and Mann-Whitney U test were used to compare continuous variables. Chi-square test was used to compare categorical variables. One-way analysis of variance (ANOVA) followed by multiple comparison test with the least significant difference was used to compare the differences among mean values of continuous variables among the subgroups (normal, mild, moderate and severe fatty liver). Differences between groups for the data that are not normally distributed variables were tested with the Kruskal-Wallis test. Stepwise multivariate logistic regression analysis was used to investigate the risk factors associated with NAFLD using the variables identified by the univariate analyses. Total cholesterol, triglyceride, non-HDL cholesterol and HOMA showed severely skewed distributions and therefore were log-transformed for statistical analysis.

Results

Of the studied participants, 4 were excluded because they tested positive for HBsAg (n = 4) or anti-HCV (n = 3). Table 1 shows the basic demographic characteristics of the remaining 216 participants. There were 134 boys and 82 girls, with an overall mean age of 12.5 years. More boys were obese than girls (41.0% versus 23.2%). Compared with girls, boys had significantly higher mean BMI, waist, and ALT levels, but lower total cholesterol and HDL-C levels. NAFLD was detected in 86 (39.8%) out of 216 participants as shown in Table 2. Among them, 54 (54/134 = 40.3%) were boys and 32 were girls (32/82 = 39.0%). Upon comparing different weight categories, the rate of NAFLD in the adolescents increased progressively from 16.0% in the normal group to 50.5% in the overweight group, and 63.5% in the obese subjects. Compared to their normal counterparts, participants with NAFLD had a significantly higher weight, BMI, waist circumference, ALT, triglyceride level as well as non-HDL cholesterol. In addition, adolescents with NAFLD had significantly elevated levels of total cholesterol and HOMA, but lower HDL cholesterol than those without NAFLD.

Table 3 depicts the clinical characteristics and weight category across the different degrees of fatty liver. There were higher ALT, HOMA-IR, cholesterol, triglyceride, and non-HDL levels as the severity of fatty liver increased. On the contrary, the HDL-C was getting lower as the severity of fatty liver increased. Among the 86 adolescents with fatty liver, only 20 (23.3%) showed an abnormality for ALT. However, there was an increasing trend of ALT abnormality as the severity of fatty liver increased. The examination of different weight categories showed that the proportion of overweight or obese adolescents increased as the severity of fatty liver increased.

Using a stepwise logistic regression model as shown in Table 4, the most significant factor associated with the development of NAFLD was the weight category. Overweight and obese adolescents had 4.14 and 5.98 times the risk of having fatty liver, respectively, when compared to their normal counterparts. Elevated ALT was the second most important factor as adolescents with elevated ALT were more likely to have NAFLD (odds ratio = 3.32, 95% CI: 1.16 to 9.50). Non-HDL cholesterol was the third most important factor associated with NAFLD, with a 3.81-fold increase in risk incurred for every l n (1 mg/dL) increment in non-HDL cholesterol.

Performing a similar stepwise logistic regression analysis as in model 2 but now excluding the weight category, HOMA-IR triglyceride and elevated ALT become significant factors associated with f NAFLD.

Conclusion

Fatty liver is an increasingly common condition frequently detected by routine abdominal ultrasonographic examination. Liver biopsy represents the best diagnostic test for fatty liver, but cannot be widely performed on apparently healthy-looking subjects for ethical reasons.

Table 2. Difference in the Selected Variables Among the Subjects With and Without NAFLD

	Male		Female		Total	
Variables	**NAFLD**	**No NAFLD**	**NAFLD**	**No NAFLD**	**NAFLD**	**No NAFLD**
No. of subjects	54	80	32	50	86	130
Number (%)						
Normal	7 (12.7%)	48 (87.3%)	8 (20.5%)	31 (79.5%)	15 (16.0)	79 (84.0)
overweight	10 (41.7%)	14 (58.3%)	14 (58.3%)	10 (41.7%)	24 (50.0)	24 (50.0)
Obese	37 (67.3%)†	18 (32.7%)	10 (52.6%)†	9 (47.4%)	47 (63.5)†	27 (36.5)
Means ± SD						
Weight (kg)	81.7 ± 16.5†	66.0 ± 14.0	64.8 ± 14.5*	56.8 ± 12.1	75.4 ± 17.7†	62.5 ± 14.0
BMI (kg/m^2)	28.9 ± 5.5†	23.2 ± 4.3	25.3 ± 4.8†	22.2 ± 4.0	27.6 ± 5.5†	22.8 ± 4.2
Waist (cm)	91.7 ± 13.3†	77.4 ± 10.8	79.5 ± 13.1†	72.0 ± 9.7	87.2 ± 14.4†	75.3 ± 10.7
ALT (IU/L)	34.7 ± 33.6†	17.6 ± 9.7	24.0 ± 26.6*	13.3 ± 6.5	30.7 ± 31.4†	15.9 ± 8.8
Cholesterol (mg/dL)	159 ± 27†	145 ± 24	168 ± 36	158 ± 28	162 ± 31†	150 ± 26
Triglyceride (mg/dL)	108 ± 61†	78 ± 44	95 ± 43†	70 ± 27	103 ± 55†	75 ± 38
HDL-C (mg/dL)	53 ± 10*	58 ± 13	57 ± 9	63 ± 14	55 ± 10†	60 ± 14
Non-HDL-C (mg/dL)	106 ± 27†	87 ± 21	111 ± 35*	95 ± 23	108 ± 30†	90 ± 22
HOMA-IR	2.1 ± 2.6†	1.0 ± 1.0	1.6 ± 1.2	1.1 ± 0.8	1.9 ± 2.2†	1 ± 0.9

ALT: alanine aminotransferase; HDL-C: high-density-lipoprotein cholesterol; Non-HDL-C: non-high-density-lipoprotein cholesterol; SD: standard deviation

*P <0.05, †P <0.005 by chi-square test, unpaired Student's *t*-test, or Mann-Whitney U test

Liver ultrasonographic scanning has a good correlation with histological findings of fatty infiltration, and has been proposed as a method of evaluation for different degrees of fatty liver. Therefore, in this study, we followed the criteria described by Needleman et al,[19] which showed an accuracy of 88% in the diagnosis and staging of fatty liver from a direct comparison between the pathological and ultrasonographic findings.

Many studies have shown that obesity and diabetes mellitus are the 2 most important risk factors for the development of NAFLD in adults.[20, 21] In the current study, it was noted that obesity was the most important factor associated with the presence of NAFLD in the adolescents. Compared with normal counterparts, overweight and obese adolescents had 4.14 and 5.98 times the risk of having NAFLD, respectively. In addition, the rate of NAFLD increased progressively from 16.0% in the normal group to 50.0% for the overweight group, and 63.5% among the obese participants. Of note, the higher ALT, HOMA-IR, cholesterol, triglyceride, and non-HDL levels and lower HDL-C as the severity of fatty liver increased indicates that a higher ALT and degree of abnormal lipid levels are predictive of severe NAFLD graded by ultrasound. In addition, the severity of fatty liver is positively associated with how overweight the subject is, in this study as well as others.[5,12] This indicates that an increased severity of obesity causes more fat to be accumulated in the liver, resulting in more severe NAFLD.

Recent studies have shown that the prevalence of childhood obesity has increased significantly in Taiwan.[22,23] It is anticipated that the global emergence of obesity in the pediatric population has made fatty liver disease a public health problem across the Western world and also the paediatric population of Taiwan.

Findings in this study were mostly consistent with other researches in that elevated ALT is a predictor of NAFLD.[9,12] In addition, it was found that there was an increasing trend of ALT abnormality as the severity of NAFLD increased. Nevertheless, only 23.3% of adolescents with NAFLD showed an abnormality in ALT. It is mentioned that serum ALT is not sensitive enough to detect low levels of hepatic fat accumulation, and heavy fat infiltration is required for abnormalities in serum aminotransferases to occur.[11] In a pediatric population, NAFLD usually affects asymptomatic healthy-looking obese children and may be difficult to detect in the early stages. It should also be stressed that the prevalence of NAFLD in our obese adolescents was as high as 63.5%, which is compatible with other studies where NAFLD was observed in 50% to 60% of obese children.[24,25] Thus, sonographic examination of the liver would seem to be a good approach to the examination of liver, because it is safe, noninvasive and an

Table 3. Clinical Characteristics and Weight Category Across Different Degree of NAFLD

Ultrasonic fatty liver	**Absent**	**Mild**	**Moderate**	**Severe**
No. of subjects	130	64	17	5
Means ± SD				
ALT (IU/L)	15.9 ± 8.8	21.4 ± 17.6	54.8 ± 47.5*†	68.6 ± 37.8*†
HOMA-IR	1.0 ± 0.9	1.4 ± 1.4	2.7 ± 3.0*†	5.5 ± 3.6*†‡
Cholesterol (mg/dL)	150 ± 26	161 ± 32*	160 ± 28	185 ± 13*
Triglyceride (mg/dL)	75 ± 38	98 ± 50*	100 ± 41*	180 ± 98*†‡
HDL-C (mg/dL)	53 ± 12	49 ± 12*	44 ± 6*	37 ± 10*†
Non-HDL-C (mg/dL)	90 ± 22	105 ± 30*	109 ± 28*	139 ± 14*†‡
Elevated ALT (>=40 IU/L)				
No	124 (95.4%)	57 (89.1%)	8 (47.1%)	1 (20.0%)
Yes	6 (4.6%)§	7 (10.9%)§	9 (52.9%)§	4 (80.0%)§
Weight category				
Normal	79 (60.8%)	14 (21.9%)	1 (5.9%)	0 (0%)
Overweight or obese	51 (39.2%)§	50 (78.1%)§	16 (94.1%)§	5 (100.0%)§

ALT: alanine aminotransferase; HDL-C: high-density-lipoprotein cholesterol; Non-HDL-C: non-high-density-lipoprotein cholesterol; SD: standard deviation

*P <0.05, versus normal, †P <0.05, versus mild fatty liver, ‡P <0.05, versus moderate fatty liver, by post-hoc test or Kruskal-Wallis test, §P value <0.001, by Cochran-Armitage trend test

Table 4. Stepwise Logistic Regression Analysis of the Presence of NAFLD in Healthy-looking Adolescents

Variable	**β**	**Odds ratio (95% CI)**	***P***
Model 1			
Overweight vs normal	1.42	4.14 (1.83-9.37)	0.001
Obese vs normal	1.79	5.98 (2.76-12.96)	<0.001
Elevated ALT (yes vs no)	1.20	3.32 (1.16-9.50)	0.02
Non-HDL-C: increased every ln (1 mg/dL)	1.34	3.81 (1.06-13.68)	0.04
Model 2			
Elevated ALT (yes vs no)	1.47	4.35 (1.58-11.96)	0.004
Triglyceride: increased every ln (1 mg/dL)	1.19	3.29 (1.585-6.86)	0.001
HOMA-IR: increased every ln (1)	0.30	1.35 (1.03-1.77)	0.032

ALT: alanine aminotransferase; HDL-C: high-density-lipoprotein cholesterol; Non-HDL-C: non-high-density-lipoprotein cholesterol; SD: standard deviation

Model 1: variables included age, sex, weight category, elevated ALT, ln (total cholesterol), ln (triglyceride), and ln (HOMA) levels.

Model 2: same variables as model 1 except weight category excluded.

easily accessible procedure. Therefore, it is suggested that ultrasonographic examination of the liver be included in the routine health check-ups of obese children to allow the detection of NAFLD at an early stage.

It is deserved discussion that although 58.2% of NAFLD in obese children was detected by ultrasonographic liver scan, whilst 41.8% of the scan showed negative finding and might be unnecessary. From a cost-effective perspective, cost for patient to receive ultrasound examination in Taiwan is about US$27 to US$35 depending on different insurance coverage, ALT examination cost US$1.50 and lipid examination US$40. The cost of ultrasonographic examination of the abdomen is low in Taiwan and it has become a regular procedure in detecting the disorders of gastrointestinal system. Thus, we recommend that ultrasonographic examination of the liver should be performed on all obese children for early detection of NFLD. As to countries with higher cost of ultrasonographic examination, we recommend using "obese children with elevated ALT" as an indication of the procedure in place of "obese children", for the cost-effectiveness.

A two-hit theory for the development of non-alcoholic steatohepatitis has been proposed.[26] The first hit leads to the development of fatty liver, and the second one result in the progression from fatty liver to NASH. Obesity, diabetes and hyperlipidaemia are the common reported first hits. Although previous studies have demonstrated that elevated triglyceride and hypercholesterolaemia are risk factors for NAFLD, it was quite interesting in the present study that non-HDL cholesterol was associated with the presence of NAFLD. Non-HDL cholesterol encompasses all cholesterol present in potentially atherogenic lipoprotein particles very-low-density-lipoprotein (VLDL), intermediate-density lipoprotein, low-density-lipoprotein (LDL) and lipoprotein[a]) and it has been shown to be a better predictor of cardiovascular death in the recent years.[27,28] From our results, non-HDL cholesterol might also be a useful marker for the development of NAFLD. The liver is a unique organ because of its capability in cholesterol metabolism and bile production. Cholesterol is excreted from the body in the bile or in a process called reverse cholesterol transport, in which HDL plays a central role. On the contrary, VLDL is produced in the liver and intestine and transformed to intermediate-density lipoprotein and LDL, and the latter can be uptake by the LDL receptor in the liver cell. As such, elevated non-HDL cholesterol, which encompasses all cholesterol except HDL cholesterol, could lead to the accumulation of lipids within hepatocyte, and it is therefore reasonable that non-HDL cholesterol might be a useful marker for a combined risk assessment for the development of NAFLD.

Insulin resistance has been shown to be associated with the development of NAFLD in obese adults and during childhood.[10,29] In this study, HOMA-IR and serum triglyceride level was associated with fatty liver in model 2, but not in model 1, when the variable of weight category was included in the analysis. The reason as to why HOMA-IR failed to be a significant factor associated with NAFLD in model 1 was due to its strong relation to obesity. The effect of HOMA-IR was masked by the effect of obesity, and once weight category was removed as a variable in model 2, the relation of HOMA-IR and NAFLD came to the fore. In clinical practice, it is not cost-effective to screen the NAFLD in the adolescents by measurement of HOMA-IR. On the contrary, it is easy to screen the obese adolescents defined by using the BMI.

Some limitations of the present study should be mentioned. Firstly, this study was of a cross-sectional design, which precludes a cause-and-effect relationship between the associated factors and the development of NAFLD. Besides, NASH is an aggressive liver disease that can lead to advanced fibrosis, cirrhosis and even hepatic failure, therefore it might be more important to have the means to diagnose and determine which of those with fatty liver with or without elevated ALT are at risk of progression to NASH. Therefore additional longitudinal studies comprising of a larger sample with varying degrees of obesity are needed to explore the cause and progression of NAFLD in a paediatric population.

Secondly, although it is a community-based study, the number of boys was much higher than girls. Therefore, caution needs to be exercised in applying our results to other communities in Taiwan. Finally, 4.6% of children without ultrasound appearance of NAFLD had elevated ALT in this study. Since we did not provide second blood test for those with abnormal ALT, therefore, we can not reject the possibility of measurement error. Same situation also occurred in the ultrasonographic examination of the liver because it is still significantly operator dependent.

In conclusion, the current study strongly indicated that obesity, ALT abnormality and elevated non-HDL cholesterol are all associated with NAFLD among the adolescents in Taiwan. In addition, the rate of NAFLD was 63.5% in our asymptomatic obese subjects, which indicates that it is a common finding among obese children and deserves attention. It is recommended that ultrasonography of the liver should be included in the routine health examinations of obese adolescents.

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