Association between the non-HDL-cholesterol to HDL-cholesterol ratio and non-alcoholic fatty liver disease in Chinese children and adolescents: a large single-center cross-sectional study

Shouxing Yang (675165854@qq.com)
Zhuji People's Hospital of Zhejiang Province https://orcid.org/0000-0002-9545-6849
Jinwei Zhong
The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University
Mengsi Ye
The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University
Lei Miao
The Second Affiliated Hospital and Yuying children's Hospital of Wenzhou Medical University
Guangrong Lu
The Second Affiliate Hospital and Yuying children's Hospital of Wenzhou Medical University
Changlong Xu
The second Affiliated Hospital and Yuying chilidren's Hospital of Wenzhou Medical University
Zhanxiong Xue
The Second Affiliated Hospital and Yuying children's Hospital of Wenzhou Medical University
Xinhe Zhou
The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University

Research

Keywords: Non-alcoholic fatty liver disease, NHDLC/HDLC ratio, Children, Adolescents, Cross-sectional study, Receiver operating characteristic curve

Posted Date: October 13th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-63438/v2

Version of Record: A version of this preprint was published on November 22nd, 2020. See the published version at https://doi.org/10.1186/s12944-020-01421-5.

Abstract

Background: The non-HDL cholesterol to HDL cholesterol (NHDLC/HDLC) ratio is closely related to a variety of dyslipidemia-related disease. This study aimed to inspect the relationship between the NHDLC/HDLC ratio and non-alcoholic fatty liver (NAFLD) in childhood and adolescence.

Methods: In this cross-sectional survey, a total of 7,759 eligible Chinese children and adolescents (5,692 boys and 2,067 girls) were received routine medical examinations. The anthropometric and laboratory data of the subjects were collected. NAFLD was diagnosed by liver ultrasonography. The binary logistics regression analysis was performed on NHDLC/HDLC ratio, NHDLC and HDLC and NAFLD. ROC curve analysis was exploited to compare the diagnostic significance of the above parameters for NAFLD.

Results: The total prevalence of NAFLD was 4.36%, and the prevalence of boys was higher than that of girls (5.61% vs. 1.9%, $P < 0.001$). The prevalence of NAFLD was positively correlated with the NHDLC/HDLC ratio ($P < 0.001$). The binary logistics regression analysis demonstrated that the OR was 8.61 (95% CI, 5.90-12.57, $P < 0.001$) in the tertile 3 (highest NHDLC/HDLC ratio) compared with the tertile 1 (lowest NHDLC/HDLC ratio). When potential confounders (age, sex, BMI, ALT, UA, TB, FPG and HOMA-IR) were adjusted, the OR for the tertile3 (OR=1.83, 95% CI, 1.04-3.22, $P = 0.035$) was still drastically higher than that of the tertile 1. The AUC of the NHDLC/HDLC ratio of boys was 0.787, which was significantly greater than that of NHDLC and HDLC (0.719 and 0.726, $P < 0.001$). For girls, the AUC of NHDLC/ HDLC ratio was 0.763, which was also significantly greater than that of NHDLC (0.661, $P < 0.001$). Furthermore, the cutoff points of NHDLC/HDLC ratio were 2.475 in boys and 2.695 in girls.

Conclusions: The NHDLC/HDLC ratio was positively correlated with NALFD in Chinese children and adolescents. It may serve as an effective indicator to help identify NALFD in children and adolescents.

Background

Non-alcoholic fatty liver disease (NAFLD), a chronic liver disease (CLD), involving fatty liver or liver steatosis and nonalcoholic steatohepatitis (NASH) [1]. Nowadays, NAFLD turn out to be the major reason for CLD in pediatric population. Given epidemiological data, the prevalence of NAFLD is 2.6–7.1% of all children and about 27.8–41.2% of obese children. Furthermore, the incidence ratio of NAFLD is on the rise [2, 3].

NAFLD is now recognized as a metabolic syndrome (MS) manifested in hepatic area, and its progressive form NASH elevating the risk of liver cancer, end-stage liver disease and cirrhosis [4]. Furthermore, pediatric NAFLD is considered to be involved in the pathogenesis of diabetes mellitus (DM), MS as well as cardiovascular disease (CVD) [5]. Since children with NAFLD are usually symptomless, the diagnosis of NAFLD in childhood and adolescence is challenging. Although the diagnostic gold standard for NAFLD is liver biopsy, it is not readily accepted by children as its invasive nature. Liver ultrasonography refers to a feasible and noninvasive mean to diagnose NAFLD, whereas not all kids undergo liver ultrasonography since their parents may be reluctant to let them receive medical examination for a clinically silent disease

[6]. Thus, valuable indicators for NAFLD should be identified for early detection and prevention of later progression.

The non-HDL cholesterol to HDL cholesterol (NHDLC/HDLC) ratio is closely related to a variety of dyslipidemia-related diseases, such as chronic kidney disease, gallbladder polyp, insulin resistance (IR) and MS. Besides, NHDLC/HDLC ratio has a better predictive value for CVD in Type 2 DM than high-density lipoprotein cholesterol (HDLC) [7-10]. A recent prospective study found that the NHDLC/HDLC ratio is more sensitive to predict NAFLD in adults than non-high-density lipoprotein cholesterol (NHDLC) [11]. However, the association between NHDLC/HDLC and NAFLD in childhood and adolescence remains unclear. Consequently, this study aims at exploring the relationship between the NHDLC/HDLC ratio and NAFLD in childhood and adolescence .

Materials And Methods

Subjects

Totally 7,759 children and adolescents received regular medical examination from January 2015 to January 2020 in our hospitals were investigated. The inclusion criteria were subjects aged 2-18 years and had liver ultrasonography. Hepatitis virus infection, metabolic liver disease, lipid -lowering agents treatment in last month, hereditary hyperlipidemia and regular alcohol consumption were excluded.

The elements of anthropometry and laboratory examinations

The clinical and anthropometric measurements assessed were age, gender, weight and height. Height and weight were examined on the same day. The body's weight (kg) dividing by the height squared (m^2) was used to determine the body mass index (BMI). As for laboratory test, under standard laboratory procedures, this study employed fasting blood samples to delve into metabolic variables. We collected the parameters of total cholesterol (TC), fasting plasma glucose (FPG), HDLC, triglycerides (TG), alanine aminotransferase (ALT), alkaline phosphatase (APL), glycated hemoglobin A1c (HbA1c), low-density lipoprotein cholesterol (LDLC), albumin (ALB), uric acid (UA), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total bilirubin (TB) and creatinine (Cr). Homeostasis Model Assessment of IR (HOMA-IR) was calculated by: HOMA-IR = FPG × fasting insulin / 22.5 [12] . Children with BMI > 95th percentile were obese [13].

Ultrasonography

The liver ultrasonography was performed by an experienced expert with a Philips En2visor26 type ultrasonic diagnostic instrument (probe frequency 3.5-5.0M*Hz*). The diagnosis of NAFLD was according to the following radiologic parameters: ultrasound signals suggested deep attenuation, vascular blurring, and discursively expanded echo (bright) liver showing echoes on kidney or spleen [14].

Statistical analysis

All date were evaluated by SPSS 21.0 (SPSS Inc.) and EmpowerStats (http:// www. empowerstats.com). Means ± standard deviations (SD) denoted continuous data. The categorical variables were described using percentages. Total participants were stratified into three tertiles according NHDLc/HDLc ratio (≤1.79, 1.80-2.36, ≥2.37). In order to evaluate the differences between groups, this study performed one-way ANOVA followed by LSD test on continuous variables with Gaussian distribution. The chi squared (χ^2) test was performed on the categorical data. The binary logistics regression analysis for variables associated NAFLD was performed. Receiver operating characteristic (ROC) curve anlysis was derived for evaluating the effectiveness of different lipid levels as indicators for NAFLD. The *P*-value for a two-tailed test < 0.05 reflected statistically significant and the figures were generated by Graphpad prism 6 project.

Results

Baseline characteristics

As showed in Fig. 1, a total of 7,759 eligible children and adolescents (5,692 boys, 2,067 girls) were recruited, the mean age of participants was 9.09 ± 3.30 and the mean BMI was 17.38 ± 3.72. Table 1 draws the comparison of the baseline characteristics by tertiles of the NHDLC/HDLC ratio. It was identified that these three tertiles had significant differences. In contrast to subjects in the tertile 3 (highest NHDLC/HDLC ratio), those in the tertile 1 (lowest NHDLC/HDLC ratio) were had lower BMI, ALT, GGT, UA, ALB, TC, TG, LDLC, HbA1c (%), FPG, HOMA-IR and higher TB, ALP and HDL (*P* < 0.001). The incidence of obesity noticeably rose across NHDLC/HDLC tertiles 1, 2 and 3 (4.81%, 9.22% and 21.18%, respectively, *P* < 0.001).

Prevalence of NAFLD and the NHDLC/ HDLC ratio

The prevalence of NAFLD was positively correlated with the NHDLC/HDLC ratio. Compared with tertiles 1 (1.2%), the tertiles 2 (2.33%, *P* < 0.001) and tertiles 3 (9.49%, *P* < 0.001) showed a significantly higher NAFLD prevalence. Compared with tertile 1, the prevalence of NAFLD in tertile 3 was nearly eight times higher (Fig. 2). In addition, the total prevalence of NAFLD was 4.36%, and the one for boys was higher than that for girls (5.61% vs. 1.9%, *P* < 0.001) (Fig. 3).

Association between the NHDLC/ HDLC ratio and NAFLD

The binary logistics regression analysis showed the Odds ratio (OR) of NAFLD was significantly elevated as the NHDLC/HDLC ratio arose. The OR was 8.61 (95% CI, 5.90-12.57, *P* < 0.001) in the tertile 3 compared with the tertile 1. When potential confounders (age, sex, BMI, ALT, UA, TB, FPG and HOMA-IR) were adjusted, the OR for the tertile3 (OR=1.83, 95% CI, 1.04-3.22, *P* = 0.035) was still drastically higher than that of the tertile 1. Moreover, the NHDLC/HDLC ratio increased by 0.9 mmol/L, and the risk of NAFLD increased by 1.89 times (OR = 1.89, *P* < 0.001). (Table 2)

The diagnostic significance of the NHDLC/ HDLC ratio for NAFLD

In order to assess the diagnostic significance of NHDLC/HDLC ratio, NHDLC and HDLC for NAFLD, this study implemented gender-specific ROC curve analysis (Fig. 4). The area under the curve (AUC) of the NHDLC/HDLC ratio was 0.787 (0.758-0.816) in boys, significantly greater than that of NHDLC (0.719, 0.687-0.751, $P < 0.001$) and HDLC (0.726, 0.698-0.755, $P < 0.001$). As for girls, the AUC of NHDLC/HDLC ratio (0.763, 0.688-0.837) was also significantly greater than that of NHDLC (0.661, 0.580-0.743, $P < 0.001$), but there was no considerable difference with HDLC (0.732, 0.663-0.802, $P = 0.239$). Furthermore, the cutoff point of the NHDLC/ HDLC ratio in boys was 2.475, exhibiting a sensitivity of 71.18% and a specificity of 74.46%. Besides, the cutoff point in girls was 2.695, exhibiting a sensitivity of 66% as well as a specificity of 80.09%.

Discussion

For the first time in this study, it was found that a high NHDLC/HDLC ratio was highly positively correlated with the prevalence of NAFLD in childhood and adolescence. Moreover, in both boys and girls, the diagnostic value of NHDLC/HDLC ratio for NAFLD was better than that of NHDLC. Therefore, it is shown that the NHDLC/HDLC ratio may help early identification of NALFD in childhood and adolescence.

Previous studies had confirmed that MS and obesity are the major risk elements for NAFLD in pediatric population and dyslipidemia play a pivotal role in NAFLD pathogenesis [4, 15]. Recent clinical assessments suggest that statin-based therapies (lipid -lowering agents treatment) could improve impaired hepatic function and evidences of live ultrasonography of patients with NAFLD [16]. The dyslipidemia in NAFLD is symbolized by increase of TG and LDLC and decrease of HDLC [17]. As driven by lipid metabolism abnormalities, excess fat in NAFLD undergoes accumulation in the hepatocytes. The mentioned intrahepatic lipid accumulating was attributed to decreased TG export, uptake of liver free fatty acid (FFA) and very low-density lipoprotein cholesterol production [18, 19]. Ectopic lipid overloading in hepatocytes are associated with an inflammation induction, oxidative stress, and the secreting numerous cytokines (including adiponectin, interleukins and tumor necrosis factor) [20]. Moreover, excess of FFA form to fatty acyl-CoAs sequentially catalyzed by fatty acyl-CoA synthetase, thereby probably inducing β-oxidation pathways. The above inflammation, oxidative stress are involved in NAFLD initiation and progression [21, 22].

NHDLC is regarded as secondary target of lipid-lowering therapeutic method, which refers to TC minus HDLC [23]. Compared with the NHDLC, the NHDLC/HDLC ratio could cover more comprehensive abilities of lipid dysregulation and better for assessing lipid metabolism-related disease risk. According to the existing study, the NHDLC/HDLC ratio is better than NHDLC in predicting the occurrence of CVD in type 2 DM [10], and the ratio exhibits a higher prediction result than the apoB/apoA1 ratio of the IR and MS [9]. Moreover, as revealed from a perspective cohort study, the NHDLC/HDLC ratio outperforms NHDLC in predicting new-onset NAFLD in Chinese adult population [11]. Therefore, it is necessary to explore the association between the NHDLC/HDLC ratio and NAFLD in the pediatric population.

Baseline characteristic data of 7,759 subjects stratified into three tertiles according NHDLC/HDLC ratio showed that anthropometric variables (such as ALT, TG, LDLC, HbA1c, FPG) were higher in the highest NHDLC/HDLC ratio tertile than in the lowest one. The similar results can be discovered in previous studies [24]. Expectantly, the incidence of obesity notably increased across NHDLC/HDLC tertiles. In addition, the prevalence of NAFLD increased while the tertiles (NHDLC/ HDLC ratio) rose. The binary logistics regression analysis suggested that higher NHDLC/ HDLC ratio was positively connected to NAFLD. In terms of gender distribution, it is found that the frequency of NAFLD by gender was significant higher in boys as compared with girls. The result of this study complies with Brunt et al [25] and Welsh et al [26]. It has been indicated this phenomenon may be attributed to the potential protective role of estrogen against hepatic steatosis [27, 28].

The findings here are of certain clinical implications. According to the AUC results, the NHDLC/HDLC ratio may be exercised as a more suitable indicator for NAFLD in childhood and adolescence than NHDLC and HDLC, especially in boys. What's more, the NHDLC/ HDLC ratio exhibits simplicity and feasibility for determination. Therefore, the NHDLC/ HDLC ratio is feasible for screening and identifying NAFLD in children and adolescents.

Study strength and limitations

As a large sample study, conclusions of the study could be more convincing and meaningful. It is firstly found that NHDLC/HDLC ratio was positively associated with NALFD among childhood and adolescents in China. The NHDLC/HDLC ratio exhibits simplicity and feasibility for determination, accordingly, the NHDLC/ HDLC ratio might be helpful for identifying NAFLD among children and adolescents.

Some limits are worth noting here. First, the NAFLD's diagnosis was performed using ultrasound instead of liver biopsy, avoiding the complications and invasiveness of liver biopsy. However, when the fat content is < 30%, the NAFLD sensitivity of ultrasonography is reduced, which may lead to misdiagnosis [29]. Second, since this was an single-center study, multi-center studies should be conducted to confirm the conclusions of this study. Third, this study adopted across-sectional designing process, so the causal relationship between the NHDLC/HDLC ratio and NAFLD cannot be determined as a whole. This correlation needs further confirmation by prospective study. Fourth, since this study only includes Chinese children and adolescents, it is incomprehensible to extrapolate the results to the other pediatric races.

Conclusions

The NHDLC/HDLC ratio is positively correlated with NALFD in Chinese children and adolescents. It may be an effective indicator to help identify NALFD in childhood and adolescence and prevent disease progression.

Abbreviations

NHDLC/HDLC: Non-HDL-cholesterol to HDL-cholesterol; NAFLD: Non-alcoholic fatty liver disease; CLD: Chronic liver disease; NASH: Nonalcoholic steatohepatitis; MS: Metabolic syndrome; DM: Diabetes millitus; CVD: Cardiovascular disease; IR: Insulin resistance; HDLC: High-density lipoprotein cholesterol; NHDLC: Non-high-density lipoprotein cholesterol; BMI: Body mass index; TC: Total cholesterol; FPG: Fasting plasma glucose; TG: Triglycerides; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; HbA1c: Glycated hemoglobin A1c; LDLC: Low-density lipoprotein cholesterol; ALB: Albumin; UA: Uric acid; AST: Aminotransferase; GGT: Gamma-glutamyl transferase; TB: Total bilirubin; Cr: Creatinine; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; OR: Odds ratio; CI: Confidence intervals; ROC: Receiver operating characteristic; AUC: Area under the curve; FFA: Free fatty acid

Declarations

Acknowledgements

Great thanks to Xinhe Zhou (Department of Endocrinology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University) for her helpful comments of the study.

Authors’ contributions

SXY and XHZ designed the study and and wrote the manuscript; MSY, GRL, LM and JWZ collected anthropometric measurements and laboratory tests data, XZX analysed the data. All authors approved the final manuscript.

Funding

The project was supported by Medical Health Science and Technology Project of Zhejiang Provincial Health Commission(No. 2019330727).

Availability of data and materials

All data used in this study are available from the corresponding Author.

Ethics approval and consent to participate

This cross-sectional study protocol obtained the approving documents from the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University (No. L-2020-21). All children’s parents provided informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Lomonaco R, Bril F, Portillo-Sanchez P, Ortiz-Lopez C, Orsak B, Biernacki D, Lo M, Suman A, Weber MH, Cusi K: Metabolic Impact of Nonalcoholic Steatohepatitis in Obese Patients With Type 2 Diabetes. Diabetes Care 2016, 39:632-638.
2. Alisi A, Feldstein AE, Villani A, Raponi M, Nobili V: Pediatric nonalcoholic fatty liver disease: a multidisciplinary approach. Nat Rev Gastroenterol Hepatol 2012, 9:152-161.
3. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A: The Prevalence of Non-Alcoholic Fatty Liver Disease in Children and Adolescents: A Systematic Review and Meta-Analysis. PLoS ONE 2015, 10:e0140908.
4. Katsiki N, Mikhailidis DP, Mantzoros CS: Non-alcoholic fatty liver disease and dyslipidemia: An update. Metab. Clin. Exp. 2016, 65:1109-1123.
5. Nobili V, Alkhouri N, Alisi A, Della Corte C, Fitzpatrick E, Raponi M, Dhawan A: Nonalcoholic fatty liver disease: a challenge for pediatricians. JAMA Pediatr 2015, 169:170-176.
6. Kim JY, Cho J, Yang HR: Biochemical Predictors of Early Onset Non-Alcoholic Fatty Liver Disease in Young Children with Obesity. J. Korean Med. Sci. 2018, 33:e122.
7. Zuo PY, Chen XL, Liu YW, Zhang R, He XX, Liu CY: Non-HDL-cholesterol to HDL-cholesterol ratio as an independent risk factor for the development of chronic kidney disease. Nutr Metab Cardiovasc Dis 2015, 25:582-587.
8. Zhao X, Zheng H, Shan S, Wang K, Zhang M, Xie S, Liu C: Association between the non-HDL-cholesterol-to-HDL-cholesterol ratio and the risk of gallbladder polyp formation among men: a retrospective cohort study. Lipids Health Dis 2020, 19:146.
9. Kim SW, Jee JH, Kim HJ, Jin SM, Suh S, Bae JC, Kim SW, Chung JH, Min YK, Lee MS, et al: Non-HDL-cholesterol/HDL-cholesterol is a better predictor of metabolic syndrome and insulin resistance than apolipoprotein B/apolipoprotein A1. Int. J. Cardiol. 2013, 168:2678-2683.
10. Lu W, Resnick HE, Jablonski KA, Jones KL, Jain AK, Howard WJ, Robbins DC, Howard BV: Non-HDL cholesterol as a predictor of cardiovascular disease in type 2 diabetes: the strong heart study. Diabetes Care 2003, 26:16-23.
11. Wang K, Shan S, Zheng H, Zhao X, Chen C, Liu C: Non-HDL-cholesterol to HDL-cholesterol ratio is a better predictor of new-onset non-alcoholic fatty liver disease than non-HDL-cholesterol: a cohort study. Lipids Health Dis 2018, 17:196.
12. Hu Y, Li L, Xu Y, Yu T, Tong G, Huang H, Bi Y, Weng J, Zhu D: Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and β-cell function in subjects with long-term remission. Diabetes Care 2011, 34:1848-1853.
13. Hill AP, Zuckerman KE, Fombonne E: Obesity and Autism. Pediatrics 2015, 136:1051-1061.
14. Farrell GC, Chitturi S, Lau GK, Sollano JD, Asia-Pacific Working Party on NAFLD: Guidelines for the assessment and management of non-alcoholic fatty liver disease in the Asia-Pacific region: executive summary. J. Gastroenterol. Hepatol. 2007, 22:775-777.

15. Fang YL, Chen H, Wang CL, Liang L: Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From "two hit theory" to "multiple hit model". World J. Gastroenterol. 2018, 24:2974-2983.
16. Athyros VG, Tziomalos K, Daskalopoulos GN, Karagiannis A, Mikhailidis DP: Statin-based treatment for cardiovascular risk and non-alcoholic fatty liver disease. Killing two birds with one stone. Ann. Med. 2011, 43:167-171.
17. Chatrath H, Vuppalanchi R, Chalasani N: Dyslipidemia in patients with nonalcoholic fatty liver disease. Semin. Liver Dis. 2012, 32:22-29.
18. Musso G, Gambino R, Cassader M: Cholesterol metabolism and the pathogenesis of non-alcoholic steatohepatitis. Prog. Lipid Res. 2013, 52:175-191.
19. Polyzos SA, Aronis KN, Kountouras J, Raptis DD, Vasiloglou MF, Mantzoros CS: Circulating leptin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Diabetologia 2016, 59:30-43.
20. Reddy JK, Rao MS: Lipid metabolism and liver inflammation. II. Fatty liver disease and fatty acid oxidation. Am. J. Physiol. Gastrointest. Liver Physiol. 2006, 290:G852-858.
21. Ferramosca A, Zara V: Modulation of hepatic steatosis by dietary fatty acids. World J. Gastroenterol. 2014, 20:1746-1755.
22. Mashek DG, Khan SA, Sathyanarayan A, Ploeger JM, Franklin MP: Hepatic lipid droplet biology: Getting to the root of fatty liver. Hepatology 2015, 62:964-967.
23. Expert Panel on Detection, Evaluation, Adults aToHBCi: Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001, 285:2486-2497.
24. Wang D, Wang L, Wang Z, Chen S, Ni Y, Jiang D: Higher non-HDL-cholesterol to HDL-cholesterol ratio linked with increased nonalcoholic steatohepatitis. Lipids Health Dis 2018, 17:67.
25. Brunt EM: Pathology of nonalcoholic fatty liver disease. Nat Rev Gastroenterol Hepatol 2010, 7:195-203.
26. Welsh JA, Karpen S, Vos MB: Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. J. Pediatr. 2013, 162:496-500.e1.
27. Liu Z, Que S, Zhou L, Zheng S: Dose-response Relationship of Serum Uric Acid with Metabolic Syndrome and Non-alcoholic Fatty Liver Disease Incidence: A Meta-analysis of Prospective Studies. Sci Rep 2015, 5:14325.
28. Ballestri S, Nascimbeni F, Baldelli E, Marrazzo A, Romagnoli D, Lonardo A: NAFLD as a Sexual Dimorphic Disease: Role of Gender and Reproductive Status in the Development and Progression of Nonalcoholic Fatty Liver Disease and Inherent Cardiovascular Risk. Adv Ther 2017, 34:1291-1326.
29. Saadeh S, Younossi ZM, Remer EM, Gramlich T, Ong JP, Hurley M, Mullen KD, Cooper JN, Sheridan MJ: The utility of radiological imaging in nonalcoholic fatty liver disease. Gastroenterology 2002, 123:745-750.

Tables

Table 1 Baseline characteristics of participants

Characteristics	NHDLC/HDLC ratio			*P* value
	Tertile 1 (≤1.79)	Tertile 2 (1.80-2.36)	Tertile 3 (≥2.37)	
Sample size	2577	2580	2602	
Age (year)	9.24 ± 3.11	9.00 ± 3.31[b]	9.03 ± 3.47	0.017
Sex, n (%)				<0.001
Girl	771 (29.92)	950 (36.82)[b]	906 (34.82)[a]	
Boy	1806(70.08)	1630(63.18)[b]	1696(65.18)[a]	
BMI (kg/m^2)	16.47 ± 2.64	17.02 ± 3.27[b]	18.64 ± 4.60[a/c]	<0.001
ALT (U/L)	15.12 ± 8.49	15.93 ± 17.55	19.27 ± 19.88[a/c]	<0.001
AST (U/L)	26.51 ± 6.75	26.64 ± 13.29	27.09 ± 13.62	0.175
ALP (U/L)	252.60 ± 78.46	242.84 ± 71.71[b]	240.50 ± 76.05[a]	<0.001
GGT (U/L)	12.29 ± 5.27	12.83 ± 6.02[b]	15.45 ± 9.98[a/c]	<0.001
TB (mmol/L)	9.88 ± 4.38	9.66 ± 4.36	9.27 ± 4.14[ac]	<0.001
Cr (μmol/L)	39.50 ± 8.75	39.31 ± 9.48	39.35 ± 10.24	0.749
UA (umol/L)	300.55 ± 69.92	305.06 ± 73.84	327.42 ± 85.44[a/c]	<0.001
ALB (g/L)	45.36 ± 2.22	45.48 ± 2.17	45.78 ± 2.33[a/c]	<0.001
TC (mmol/L)	4.09 ± 0.63	4.27 ± 0.65[b]	4.62 ± 0.82[a/c]	<0.001
TG (mmol/L)	0.77 ± 0.30	0.89 ± 0.36[b]	1.21 ± 0.64[a/c]	<0.001
HDLC (mmol/L)	1.67 ± 0.29	1.39 ± 0.22[b]	1.17 ± 0.21[a/c]	<0.001
LDLC (mmol/L)	1.90 ± 0.45	2.31 ± 0.46[b]	2.79 ± 0.67[a/c]	<0.001
HbA1c (%)	5.43 ± 0.29	5.43 ± 0.27	5.46 ± 0.29[a/c]	0.001
FPG (mmol/L)	4.68 ± 0.39	4.70 ± 0.38	4.73 ± 0.37[a/c]	<0.001
HOMA-IR	1.42 ± 1.28	1.67 ± 1.93[b]	2.16 ± 2.07[a/c]	<0.001
Obesity [n(%)]	124 (4.81%)	238 (9.22%)[b]	551 (21.18%)[a/c]	<0.001

Data were expressed as the mean ± SD or percentage

a: $P < 0.05$, tertile 3 compared with tertile 1

b: $P < 0.05$, tertile 2 compared with tertile 1

c: $P < 0.05$, tertile 3 compared with tertile 2

Table 2 ORs for NAFLD by NHDLC/HDLC ratio

NHDLC/HDLC ratio	Crude			Adjusted*		
	β	OR (95% CI)	*P*	β	OR (95% CI)	*P*
Tertile 1 (≤1.79)		1			1	
Tertile 2 (1.80-2.36)	0.67	1.96 (1.16-3.03)	0.002	0.07	1.07 (0.57-2.04)	0.824
Tertile 3 (≥2.37)	2.15	8.61 (5.90-12.57)	0.000	0.61	1.83 (1.04-3.22)	0.035
Per IQR (=0.9)	1.06	2.88 (2.58-3.22)	0.000	0.63	1.89 (1.52-2.34)	0.000

Data are coefficient (B), odds rates (OR) and 95% confidence intervals (CI), *P* value

Adjusted* for age, sex, BMI, ALT, UA, TB, FPG and HOMA-IR

Figures

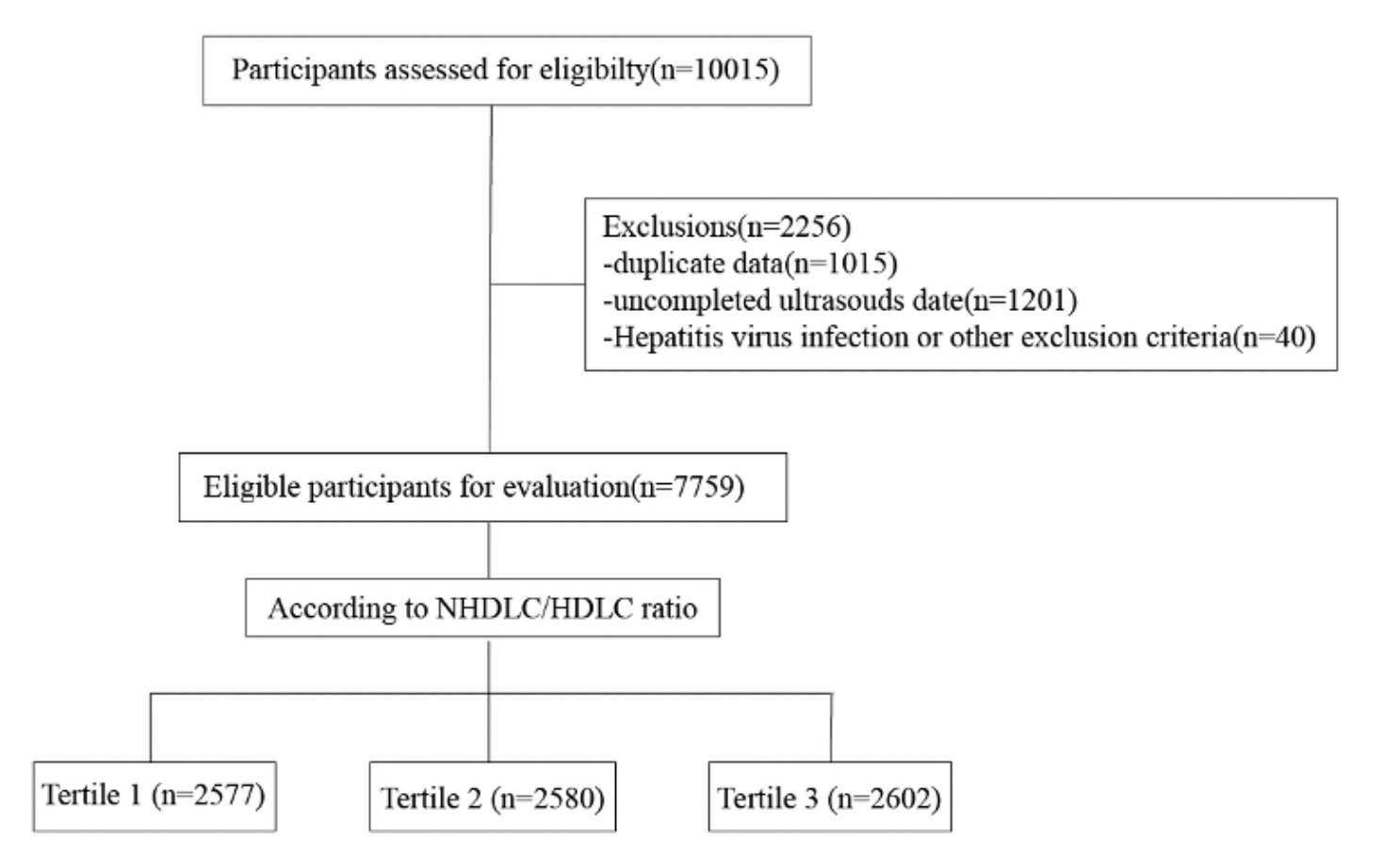

Figure 1

Flowchart of participants selection for the study

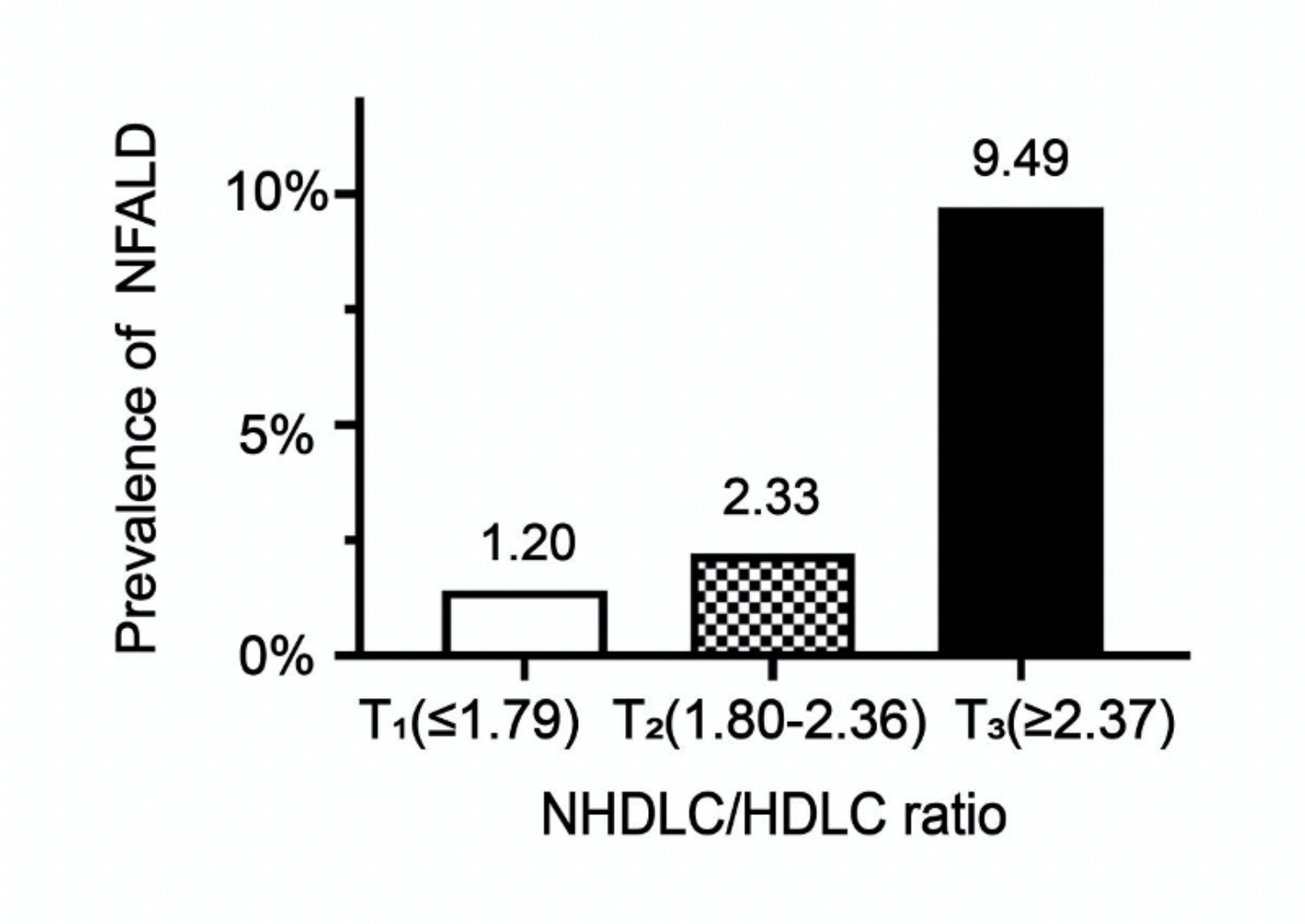

Figure 2

The prevalence of NAFLD according to the NHDLC/HDLC ratio tertiles

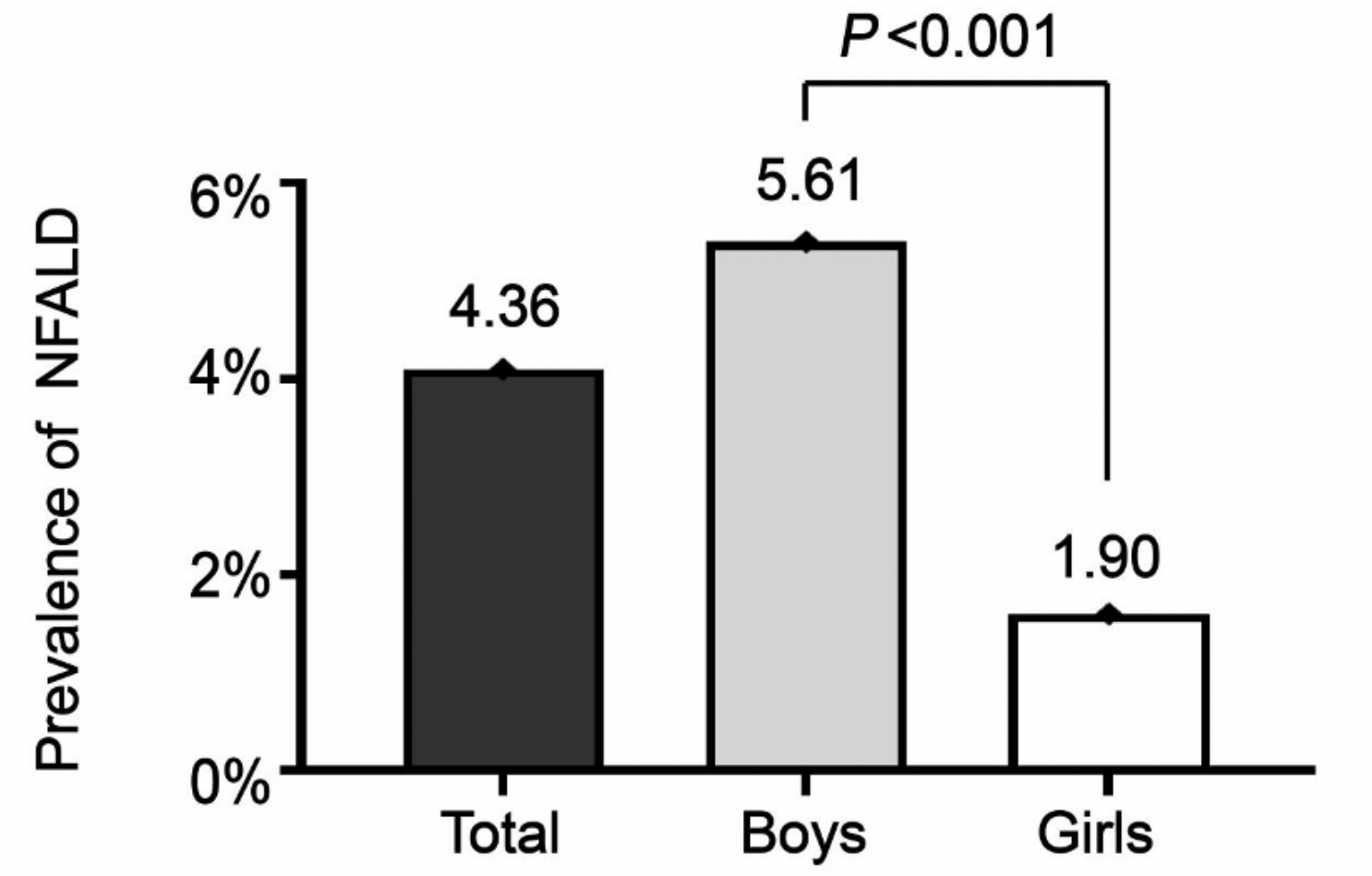

Figure 3

The prevalence of NAFLD of boys compared to girls

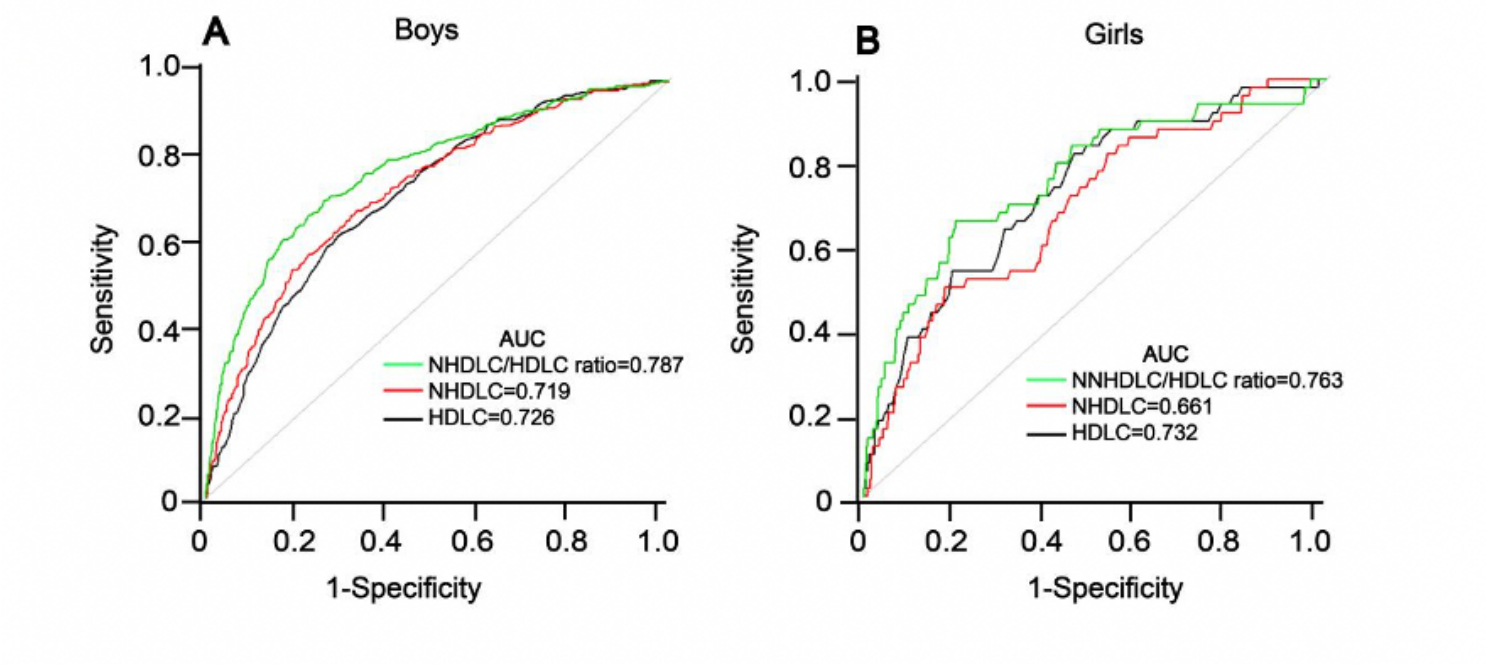

Figure 4

ROC curves of NHDLC/NHDLC ratio, HDLC and NHDLC for NAFLD in boys (A) and girls (B)