Influence of Gender, Race, and Ethnicity on Suspected Fatty Liver in Obese Adolescents

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ABSTRACT. *Objectives.* **Fatty liver is a common cause of liver disease in children. However, the epidemiology of pediatric fatty liver is limited to single-center case series of nonalcoholic fatty liver disease (NAFLD). Obesity and insulin resistance are major established risk factors for NAFLD. The role of gender, race, and ethnicity on the prevalence of fatty liver in obese children is unknown.**

Methods. **We recruited obese 12th-grade participants from the Child and Adolescent Trial for Cardiovascular Health in California, Louisiana, Minnesota, and Texas. Serum samples were collected at school when the participants were well. Alanine aminotransferase (ALT) was measured by kinetic enzymatic assay, and ALT >40 U/L was defined as abnormal. Causes of abnormal ALT other than NAFLD were excluded by serum testing.**

Results. **A total of 127 obese students (73 female, 54 male) had a mean BMI of 35.2 kg/m². Unexplained ALT elevation was present in 23% of participants overall. The mean ALT for participants with normal values was 28 U/L and for participants with an abnormal ALT was 56 U/L. Abnormal ALT was significantly more prevalent in boys (44%) than in girls (7%). The prevalence of abnormal ALT differed significantly by race and ethnicity (Hispanic: 36%; white: 22%; black: 14%). Serum ALT value was significantly predicted by the combination of gender, race/ethnicity, and BMI. After controlling for gender and BMI, Hispanic ethnicity significantly predicted greater ALT than black race.**

Conclusions. **In a national, school-based sample of obese adolescents, boys were 6 times more likely than girls to have an unexplained elevated ALT. Given that participants were well and causes of chronic liver disease were excluded, we speculate that obese adolescent boys have an increased prevalence of fatty liver compared with obese adolescent girls. This population-based study also supports the hypothesis that NAFLD is more common in Hispanic adolescents. These findings have implications for both disease screening and studies of fatty liver pathophysiology.** *Pediatrics* **2005;115:e561–e565.**

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Accepted for publication Nov 22, 2004.
doi:10.1542/peds.2004-1832
This work was presented in abstract form at the annual meeting of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition; October 2, 2003; Montreal, QC, Canada.
No conflict of interest declared.

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URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1832; ***obesity, aminotransferase, nonalcoholic fatty liver disease, steatohepatitis, Hispanic American.***

ABBREVIATIONS. NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ALT, alanine aminotransferase; CATCH, Child and Adolescent Trial for Cardiovascular Health; AST, aspartate aminotransferase.

Nonalcoholic fatty liver disease (NAFLD) is regarded as the most common cause of liver disease in children.[1] NAFLD encompasses a range of liver histology severity and outcomes in the absence of chronic alcohol use. The most mild form is simple steatosis in which triglyceride accumulates within hepatocytes. A more advanced form of NAFLD, nonalcoholic steatohepatitis (NASH), includes inflammation and liver cell injury. NASH was first described in children in 1983,[2] and more recently, several investigators have reported that NASH may present with cirrhosis and end-stage liver disease in some children.[3–6] Established risk factors for NAFLD in children include obesity, insulin resistance, and type 2 diabetes.[5,7,8]

Although most pediatric patients with NAFLD are obese, only a subset of obese children or adolescents will develop NAFLD. Gender is likely to be 1 important factor that modifies the risk for NAFLD. Early studies in adults suggested that women were more likely than men to have NASH.[9–11] Furthermore, women continue to outnumber men in clinical reports of NAFLD. However, some clinical series of NASH and epidemiologic studies of NAFLD suggest that men are at least as likely as women to have NAFLD.[12,13] The influence of gender on the prevalence of NAFLD in children remains unclear. Clinical series of children with NAFLD uniformly demonstrate a predominance of boys versus girls.[2,3,5,14–16] Whether the gender distribution of pediatric patients with NAFLD accurately reflects the predominance of NAFLD in boys over girls or represents a selection bias is unknown.

Clinical series of pediatric NAFLD have included predominantly children of white or Asian race, possibly reflecting the community demographics of reporting centers. Clinical series restricted to the southwestern United States raise the possibility that Mexican American children have higher rates of NAFLD than non-Hispanic children.[5,17] Although black children are known to have high rates of risk

factors for NAFLD, such as obesity and insulin resistance,[18–21] few children of black race are included in clinical series of NAFLD.[5] Whether black children have lower rates of NAFLD or, alternatively, have NAFLD that remains undiagnosed is unknown.

A better understanding of the influence of gender, race, and ethnicity may provide additional insight into the pathophysiology of NAFLD. An additional goal is to limit unrecognized biases in health care delivery to children. We sought to test the hypotheses that obese adolescent boys are more likely to have NAFLD than obese adolescent girls and that obese Hispanic adolescents are more likely to have NAFLD than obese non-Hispanic adolescents. We used elevated serum alanine aminotransferase (ALT) as a surrogate for suspected fatty liver in obese adolescents after excluding other causes for abnormal serum ALT.[22] To reduce selection bias, we used a large, regionally diverse, school-based cohort.

METHODS

Study Design and Cohort Selection

The participants for this study were part of a larger study, the Child and Adolescent Trial for Cardiovascular Health (CATCH). The CATCH project was the largest school-based randomized trial ever conducted. The baseline CATCH cohort was recruited in 1991–1992 from 96 public elementary schools (third grade) located in California, Louisiana, Minnesota, and Texas. The design and results of the trial are described in detail elsewhere.[23–27] Longitudinal follow-up was conducted on the original CATCH cohort during grade 8 and grade 12. Twelfth-grade students (n = 2575) who were enrolled in the CATCH study at the time of final measurement and serum collection, November 2000 to June 2001, were considered eligible for this study. By using 12th-grade students exclusively, we were able to control for age and to avoid the potentially confounding role of puberty that would be present in a younger sample. The racial distribution was white (71%), black (13%), Hispanic (13%), and other (3%). As the sera were not anonymous and previously collected data were available for analysis, participants were required to provide a new consent.

We sought to determine the presence or absence of fatty liver in obese adolescents to test the hypotheses that among obese adolescents, boys are more likely to have NAFLD than girls and that Hispanic adolescents are more likely to have NAFLD than non-Hispanic adolescents. In late adolescence, the boundaries between pediatric and adult definitions of obesity begin to blur. According to the World Health Organization, obesity for someone ≥18 years of age begins at a BMI of 30 kg/m^2. For 12th-grade students 17 to 18 years of age, using the age- and gender-based Centers for Disease Control and Prevention criteria, the cut point for obesity (range: 28.3–30.4 kg/m^2) may be below or above the World Health Organization criteria for adults. The International Obesity Task Force criteria[28] are very similar to the World Health Organization criteria such that for a 17.5-year-old girl, obesity would begin at a BMI of 29.8 kg/m^2. Given the potential confusion among the 3 systems we chose to use a BMI ≥30 kg/m^2 as the definition of obesity. Thus, all participants with a BMI ≥30 kg/m^2 were asked for additional consent to have their stored serum samples analyzed. In 12th grade, 345 (13.4%) CATCH participants were obese. This prevalence is within the range of other national surveys.[21] We obtained consent from 133 of the obese adolescents representing all 4 CATCH sites (Louisiana: 50; Minnesota: 32; California: 29; and Texas: 18). The protocol was approved by the institutional review boards of the University of California, San Diego; Tulane University; University of Minnesota, Minneapolis; and the University of Texas, Houston.

Physical Examination and Blood Collection

Height was measured using a portable stadiometer, and weight was measured using the SECA Integra 815 portable scale (SECA, Rumilly, France). Weight status was defined as mild obesity (BMI 30–34.9), moderate obesity (BMI 35–39.9), and severe obesity (BMI ≥40).[29,30] Serum samples were collected at school when the children were free of acute illness. Nonfasting blood samples were obtained via venipuncture with the child seated. Whole blood was collected into serum separator tubes and allowed to clot in a covered container for 20 minutes at room temperature. Clotted blood samples then were placed on ice and centrifuged for ~2 to 4 hours after blood collection. Serum was shipped by overnight carrier on refrigerant packs to the central laboratory for immediate analysis. Remaining serum was covered from light and frozen at −70°C. All assays for the current study were performed using stored sera.

Serum Aminotransferase Measurement and Exclusion of Chronic Hepatitis

As serum ALT is the most commonly used screening tool used to detect NAFLD, we used this as a surrogate for suspected fatty liver.[22] ALT and aspartate aminotransferase (AST) were measured using a standard automated kinetic enzymatic assay. Although there is no single standard cut point for abnormal serum aminotransferase, the most commonly used criterion is a value >40 U/L.[31] Therefore, elevated liver chemistry was defined as ALT or AST >40 U/L. To strengthen the use of ALT as a surrogate for fatty liver, we attempted to exclude other causes of chronic hepatitis, including hepatitis B (hepatitis B surface antigen), hepatitis C (anti–hepatitis C antibody), α-1-anti-trypsin deficiency (serum α-1-anti-trypsin level), autoimmune hepatitis (antinuclear antibody), and Wilson's disease (serum ceruloplasmin).

Data Analysis

Means, SDs, and percentages were calculated for descriptive summary statistics. Differences in prevalence of abnormal ALT between groups were determined with χ^2 tests, Fisher exact tests, and logistic regression. Logistic regression was used for testing models of serum ALT level. Statistical significance was defined as $P < 0.05$.

RESULTS

Demographics and Clinical Characteristics

Of the 133 participants who consented, 128 had sufficient serum available for analysis. One participant with an elevated ALT was excluded from further analysis because of a positive antinuclear antibody titer of 1:256. All other participants had negative testing for hepatitis B, hepatitis C, and autoimmune hepatitis with normal serum values of α-1-anti-trypsin and ceruloplasmin. Therefore, the

TABLE 1. Clinical Characteristics of the Study Population

	All Participants (n = 127)	Girls (n = 73)	Boys (n = 54)	ALT ≤ 40 (n = 98)	ALT > 40 (n = 29)
Weight, kg	101.8 (16.8)	95.5 (13.6)	110.3 (17.1)	98.3 (14.7)	114.4 (18.4)
Height, cm	170.0 (9.2)	164.8 (6.4)	177.0 (7.6)	168.8 (9.0)	174.2 (8.5)
BMI, kg/m^2	35.2 (4.6)	35.1 (4.3)	35.2 (4.9)	34.5 (4.0)	37.7 (5.5)
Systolic blood pressure, mm Hg	122 (11)	118 (8)	129 (11)	120 (10)	128 (12)
Diastolic blood pressure, mm Hg	58 (8)	57 (9)	60 (8)	57 (9)	61 (8)
Total cholesterol, mg/dL	174 (29)	179 (28)	167 (29)	175 (30)	168 (29)

All data are shown as mean (±SD).

final analysis included 127 participants of which 57% were girls and 43% were boys (Table 1). The mean age was 17.3 ± 0.2 years. The racial/ethnic distribution was similar to that of the total CATCH population: white, 67%; black, 22%; and Hispanic, 14%. The majority (70%) of participants were already obese when assessed in fifth grade. When measured in eighth grade, 86% of girls and 83% of boys were obese. By study design, all participants were obese in the 12th grade, with a mean BMI of 35.2 ± 4.6 kg/m^2. There was no difference in BMI between girls and boys.

Liver Chemistry

Unexplained ALT elevation was present in 23% (29 of 127) of participants. The mean serum ALT activity was 35 ± 14 U/L. When participants were separated into groups on the basis of normal and abnormal ALT, the mean values were 28 ± 6 U/L and 56 ± 14 U/L, respectively. Mean AST was 24 ± 8 U/L. AST was abnormal in 8 participants and in only 1 case was there an abnormal AST with a normal ALT.

Influences on ALT

In support of our first hypothesis, Fig 1A illustrates that an unexplained abnormal ALT was significantly ($P < .0001$) more common in obese boys (24 of 54) than obese girls (5 of 73). Our second hypothesis was also supported (Fig 1B) as the highest rate of elevated ALT was seen in Hispanic adolescents (36%) compared with white (22%) or black (14%) adolescents ($P < .01$). There was no significant difference in the rate of an abnormal ALT or the absolute ALT level on the basis of the duration of obesity, the state of residence, total cholesterol, or systemic blood pressure. However, the severity of obesity did influence the serum ALT level. As shown in Fig 2, mean ALT significantly increased with each category of obesity: mild, moderate, and severe. A multivariate model significantly ($P < .0001$) predicted serum ALT level using the combination of gender, race/ethnicity, and BMI and accounted for 35% of the individual variance (Table 2). After controlling for gender and BMI, Hispanic ethnicity significantly ($P < .05$) predicted greater ALT than black race.

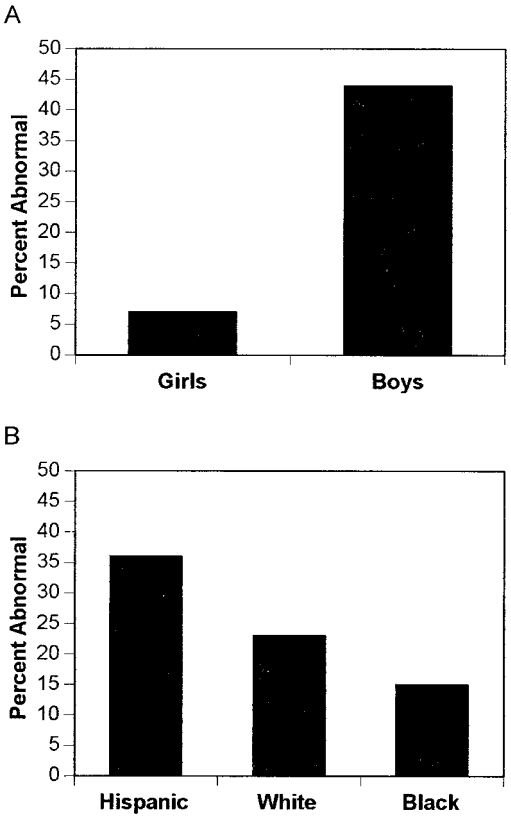

Fig 1. Prevalence of unexplained ALT elevation in obese 12th-grade students by gender (A) and race/ethnicity (B).

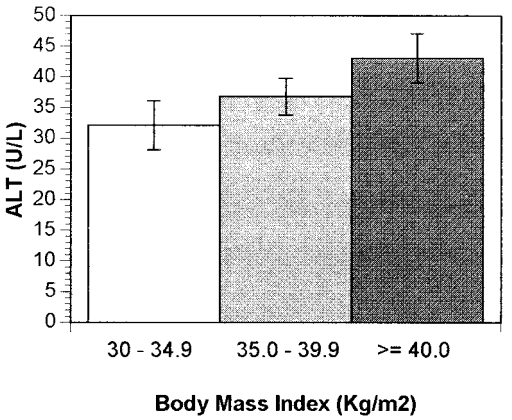

Fig 2. Mean serum ALT activity is shown by BMI category ($P < .01$). Error bars reflect SD.

DISCUSSION

We conducted a geographically diverse, population-based study of obese 12th-grade students in whom we measured liver chemistry and tested for potential causes of chronic hepatitis. The data demonstrate that the major demographic risk factors for abnormal liver chemistry among obese adolescents are male gender and Hispanic ethnicity. This finding is consistent with clinical series that use abnormal ALT either as a surrogate for NAFLD or as a criterion for liver biopsy in those with histologically proven NAFLD.

In case reports of children with NAFLD, boys outnumber girls usually in a 2:1 ratio.[16] In the majority of case reports of adults with NAFLD, women outnumber men in a 1.5:1 ratio. The data from the current study support the contention that NAFLD is more common in boys than in girls. Furthermore, given that our participants were on the cusp of crossing into adulthood, it is likely that young men have higher rates of NAFLD than young women. This is supported by epidemiologic data from the Third National Health and Nutrition Examination Survey.[13] Therefore, pediatric clinical series of NAFLD may

TABLE 2. Multivariate Model of Serum ALT Value

Variable	*P* Value
Gender	<.0001
Race/ethnicity	<.05
BMI	<.0001

The overall model is significant with $P < .0001$ and $R^2 = 0.35$.

more closely reflect the epidemiology of fatty liver than clinical series of adults with NAFLD in part because men are less likely to seek medical care than women. The awareness that many adolescents with unrecognized liver disease transition from pediatric medical care to adult health care providers represents a public health and primary care challenge.

One explanation for higher rates of fatty liver in male than in female individuals is that male individuals are more likely to distribute excess body fat in the intra-abdominal compartment. The portal hypothesis states that the complications of obesity are attributable to accumulation of visceral adipose tissue in the mesentery and omentum.[32] A majority of studies in adults demonstrate a relationship between the amount of visceral adipose tissue and presence of hepatic steatosis.[33–37] This hypothesis has not yet been tested in the pediatric age range.

Another potential reason for a gender-based difference in fatty liver development is the influence of sex hormones. Sex hormones effect the distribution of both fat and muscle. Sex hormone binding globulin, produced in the liver, is strongly correlated with insulin sensitivity.[38,39] In polycystic ovary syndrome, a decrease in sex hormone binding globulin leads to increased levels of free, metabolically active androgens.[40] Women with polycystic ovary syndrome, particularly in association with hyperandrogenism, have been shown to be at an increased risk for NAFLD.[41]

The proportion of Mexican American children in San Diego who receive a diagnosis of NAFLD far exceeds the community's ethnic demographics.[5] The current data support the belief that obese Hispanic adolescents are more likely than obese non-Hispanic adolescents to develop fatty liver. This is consistent with data from the Third National Health and Nutrition Examination Survey showing that an elevated ALT is more common in Mexican American adults.[13] The importance of such findings is reinforced by data showing that Hispanic adults have an increased rate of liver-related morbidity and mortality.[42] Cryptogenic cirrhosis is 3 times more prevalent in Hispanic Americans than European Americans and 4 times less prevalent in African Americans than European Americans.[43] Nonalcoholic steatohepatitis is the most common cause of cryptogenic cirrhosis and thus is likely a major contributor to racial and ethnic differences in liver disease.[44,45] Our data showing a lower rate of suspected fatty liver in obese black adolescents are consistent with a large clinical series of adults with NASH.[46] We speculate that blacks either have a protective factor, making fatty liver less common, or lack a vulnerability factor for the development of fatty liver.

We recognize limitations to the current study. There may be some loss of aminotransferase activity in frozen sera.[47] Any potential error introduced should apply equally without respect to gender, race, or ethnicity. This may have led to an underestimation of ALT abnormality. Furthermore, we measured liver chemistry at a single point in time. Serum ALT may fluctuate over time, influencing the prevalence estimates for abnormal liver chemistry but would not be expected to change the relationships between groups. We acknowledge that abnormal ALT alone does not prove fatty liver, but several lines of reasoning support the contention. The first is that in obese children, an elevated ALT is a strong predictor of fatty liver.[48] Second, among obese adults with a BMI $\geq$35 kg/m^2, having an ALT $>$40 U/L is a strong independent risk factor for NASH.[49] In addition, we did test for many other potential explanations for an abnormal ALT. Although serum samples were collected from students during school, we cannot exclude chronic alcohol use as a contributor to elevated ALT. Furthermore, some subjects may have fatty liver despite having an ALT within the "normal" range.[50] Finally, the current study did not include young children; children who were overweight but not obese; and children who were not white, black, or Hispanic. For example, the role of race was not addressed in some populations that also have increased rates of insulin resistance, including Asians, Pacific Islanders, and Native American Indians.

In conclusion, in a population-based study of obese adolescents, we demonstrated that suspected fatty liver is more common in boys than in girls and in Hispanics than in non-Hispanics. As a majority of chronic liver disease is asymptomatic, such data should prove useful in developing models for disease screening.[51,52] In addition, the current data raise questions to be answered in subsequent studies. A histology-based epidemiology study would further add to our understanding of the influence of gender, race, and ethnicity on the prevalence of fatty liver. Moreover, detailed metabolic and genetic studies in obese children with and without fatty liver should focus on differences between boys and girls as well as children of different race and ethnicity.

ACKNOWLEDGMENTS

The current study was supported by a grant from the Rest Haven Foundation and by grant M01 RR00827 from the National Center for Research Resources of the National Institutes of Health for the General Clinical Research Center at the University of California, San Diego.

We thank the CATCH Collaborative Research Group, including Deana Hoelscher, Russell Luepker, Philip R. Nader, Voula Osganian, Lyn M. Steffen, and Larry S. Weber, for efforts to make this study possible. CATCH was funded by cooperative agreement grants from the National Heart, Lung, and Blood Institute of the National Institutes of Health.

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Pediatrics 2005;115;e561
DOI: 10.1542/peds.2004-1832

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