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Serum Alanine Aminotransferase Trends and Their Relationship with Obesity and Metabolic Syndrome in United States Adolescents, 1999–2014

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Abstract

Introduction: Nonalcoholic fatty liver disease (NAFLD), characterized by hepatocyte dysfunction, fat accumulation, and fibrosis, is the most common cause of chronic liver disease in children. Elevated levels of serum alanine aminotransferase (ALT) are used clinically to identify potential liver dysfunction. Our goal was to assess for changes in the national prevalence of elevated ALT over time and potential relationship to trends in the metabolic syndrome (MetS) severity and elevated body mass index (BMI).

Materials and Methods: We studied 5411 non-Hispanic white, non-Hispanic black, and Hispanic adolescents aged 12–19 with complete MetS Z-score and ALT data from the National Health and Nutrition Examination Survey 1999–2014. Elevated ALT levels were defined by two different cutoffs: one for both sexes (30 U/L) and another that was sex specific (22 U/L girls; 25 U/L boys). MetS severity was assessed using a sex- and race-/ethnicity-specific MetS Z-score.

Results: We did not find a statistically significant linear increase in either mean ALT or the prevalence of elevated ALT differed over time. As expected, ALT levels were significantly correlated with BMI Z-score and MetS Z-score ($P < 0.0001$). Over time, BMI Z-scores increased and MetS severity Z-score decreased.

Conclusion: Prevalence of elevated ALT did not exhibit a linear change between 1999 and 2014 in U.S. adolescents, potentially due to divergent trends regarding BMI and MetS severity. Continued vigilance in monitoring BMI and ALT levels is advised for the U.S. adolescent population. MetS Z-score could act as an additional tool to monitor risk of elevated ALT and subsequent development of NAFLD.

Keywords: nonalcoholic fatty liver disease, alanine aminotransferase, obesity, metabolic syndrome, adolescent

Introduction

Nonalcoholic fatty liver disease (NAFLD) is a condition characterized by pathological changes to liver structure and function, including hepatocyte dysfunction, fat accumulation, and fibrosis.[1,2] If left undiagnosed or untreated in the pediatric population, NAFLD could yield poor health outcomes in adulthood, including cirrhosis and cancer.[3,4] As NAFLD is now the most common liver disease in children and adolescents, being found in ~7.6% of the U.S. adolescent population,[5] it is of utmost importance to understand the pathophysiology of NAFLD for earlier prevention. The gold standard for diagnosis of NAFLD is liver biopsy; however, the invasiveness of this procedure has led to the use of other approaches to identify risk for NAFLD.[6]

Serum alanine aminotransferase (ALT) is a liver enzyme used to evaluate liver dysfunction and serves as a screening tool for the detection of possible chronic liver disease.[7–9] While ALT has limitations in accurately identifying NAFLD,[10–13] there are numerous studies validating its use to identify fatty liver disease in adolescents, and serve as a warning sign for cardiometabolic risk factors.[14–20] It has even been shown that lowering ALT thresholds below levels commonly used in United States hospitals yielded better sensitivities in detecting chronic liver disease in children, with little compromise in specificity.[19] In surveys of healthy

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U.S. adolescents, the prevalence of increased serum ALT, which differs significantly by age, gender, and race/ethnicity,[21] ranges between 2% and 8%, depending on gender and ALT cutoff used.[19]

The metabolic syndrome (MetS) is a cluster of multiple cardiovascular risk factors, including elevated waist circumference (WC), hypertension, elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C), and elevated fasting glucose. Features of MetS have been strongly associated with NAFLD[4] and elevated ALT.[22] There is also evidence that conditions subsequent to MetS, like hypercholesterolemia and type 2 diabetes mellitus (T2DM), may also have a relationship to NAFLD.[3,23] Individual MetS components or related factors like increased body mass index (BMI), WC, hypertriglyceridemia, and insulin resistance are associated with the development of NAFLD.[7,18,24]

Previously, we found that among U.S. adolescents over the period of 1999–2012, the severity of MetS decreased, while BMI Z-scores increased.[25] The goal of this study was to assess trends in ALT over time in the U.S. adolescent population and evaluate potential upstream factors related to ALT elevations, including MetS severity and elevated BMI. We hypothesized that over time, ALT levels and ALT elevations would be found to increase to mirror the trends of increasing BMI Z-scores. We also hypothesize that in the adolescent population, ALT would be significantly correlated with the BMI Z-score, MetS Severity Score (MetS-Z), and individual components of MetS. Such knowledge may help in addressing NAFLD-related needs among adolescents.

Methods

Data were sourced from the Center for Disease Control National Health and Nutrition Examination Survey (NHANES), a nationally representative sample of the U.S. population. This study was approved by the National Center for Health Statistics Research Ethics Review Board and all participants gave informed consent or assent. We analyzed data between 1999 and 2014 in adolescents 12–19 years of age. Laboratory assessments used in our analyses have been described previously.[22] We included participants with complete data regarding MetS factors and ALT measurements. Out of 14,775 adolescents evaluated in NHANES between 1999 and 2014, 5019 met all inclusion criteria for this study. The majority of participants were excluded as a result of nonfasting status for laboratory measures, leading to missing data for MetS Z-score ($n=1925$). Participants were also excluded if they were pregnant ($n=181$), diagnosed with diabetes ($n=73$), had missing ALT values ($n=1925$), had the Hepatitis B surface antigen ($n=11$), or had missing weight. In total, 9364 participants were noneligible, with many participants meeting multiple exclusion criteria (Supplementary Fig. S1; Supplementary Data are available online at www.liebertpub.com/met). The yearly breakdown of our participant pool was similar to prior analyses.[25] Our final pool of participants ($n=5411$) was weighted to be nationally representative of U.S. adolescents based on survey design and fasting status.

ALT and cutoffs

We used two different sets of ALT cutoffs to identify elevated ALT values, as no consensus cutoff exists. The first, 30 U/L, has been commonly used in the literature as the upper limit for ALT.[7,26] The other set was derived from the SAFETY Study, which determined cutoff values of 22 U/L for females and 25 U/L for males. Using these values to detect NAFLD resulted in higher sensitivity with relatively little reduction in specificity.[19,21]

An elevated BMI Z-Score was defined as greater than or equal to the 85th percentile, also classified as ''overweight''. An elevated MetS Z-score was defined as greater than Z-score = 0.75.[27]

MetS classification and severity

The MetS severity Z-score used in our sample accounts for race-/ethnic- and sex-specific differences in MetS[27,28] that may be important in determining racial/ethnic differences in how MetS relates to ALT elevations.[22,29,30] To derive this set of scores, confirmatory factor analysis was performed using data from NHANES 1999–2010 separately for male and female non-Hispanic-white, non-Hispanic-black, and Hispanic adolescents aged 12–19 years, yielding differential loading factors for each MetS component among these six sex- and race-/ethnicity-specific subgroups. These loading factors were then used to generate equations for each sex and racial/ethnic subgroup with weights for each MetS component based on how MetS was manifested in that subgroup. These equations[31] were used to calculate the MetS Z-scores. This MetS Z-score linked with long-term risk of developing MetS-related conditions in adulthood.[25,27]

In addition, MetS was defined using a commonly used pediatric/adolescent adaptation of traditional adult criteria.[32,33] Participants had to meet ≥3 of the following five criteria: concentration of triglycerides ≥110 mg/dL, HDL-C ≤40 mg/dL, WC ≥90th percentile for age/sex[34] glucose concentration ≥100 mg/dL, and systolic or diastolic blood pressure ≥90th percentile (age, height, and sex specific).[35]

Statistical analysis

Statistical analysis was performed using SAS (SAS 9.4, Cary, NC) survey procedures to account for the complex survey design of NHANES. Values for fasting triglycerides and serum ALT were log-transformed to yield a normal distribution. Frequency procedures, chi-square testing, and regression analysis were used to assess prevalence, correlations, and significant differences between groups. Logistic regression was used to estimate odds ratios (OR). Significance was determined at a 95% confidence level, $P<0.05$. In our analyses, we looked at trends of ALT, BMI-Z, and MetS-Z; this included prevalence of elevated values as well as mean values over time. In addition, the relationships of ALT with BMI-Z and MetS-Z were assessed.

Results

Our final sample consisted of 5019 participants; 51.5% were male and the mean age, 15.5 years. Overall, the mean ALT value was 19.4 U/L; mean ALT values varied across racial ethnic groups and were 19.1 U/L, among non-Hispanic whites, 17.5 U/L, among non-Hispanic blacks, and 21.8 U/L, among Hispanics (Table 1). In our weighted sample between 1999 and 2014, only 481 individuals (9.14%) had elevated ALT levels as defined by a cutoff of

Table 1. Participant Characteristics, Weighted to Be Nationally Representative

	Non-Hispanic white	*Non-Hispanic black*	*Hispanic*	*Total*
Number	1472	1532	2015	5019
% Male[a]	51.56 (48.67, 54.44)	50.57 (47.40, 53.74)	52.02 (49.03, 55.01)	51.50 (49.42, 53.57)
Mean age in years[b]	15.51 (15.38, 15.65)	15.45 (15.32, 15.58)	15.35 (15.22,15.49)	15.47 (15.38, 15.57)
Mean BMI-Z[b]	0.53 (0.47, 0.59)	0.79 (0.71, 0.86)	0.73 (0.65, 0.81)	0.61 (0.56, 0.65)
Mean ALT in U/L[b]	19.14 (18.66, 19.63)	17.52 (17.02, 18.02)	21.75 (20.79, 22.72)	19.41 (19.02, 19.79)
% Elevated ALT[a]	8.74 (6.94, 10.54)	5.49 (3.98, 7.00)	13.33 (11.45, 15.20)	9.14 (7.86, 10.43)
Mean MetS Z-score[b]	–0.02 (–0.06, 0.03)	–0.14 (–0.19, –0.09)	0.09 (0.03, 0.14)	–0.02 (–0.05, 0.02)
% ATP III MetS prevalence[a]	7.89 (6.25, 9.53)	4.41 (3.23, 5.59)	9.90 (8.25, 11.55)	7.77 (6.60, 8.90)
% Elevated BP[a]	6.75 (5.18, 8.33)	12.05 (10.29, 13.80)	6.56 (4.99, 8.13)	7.52 (6.34, 8.71)
% Elevated fasting glucose[a]	14.04 (11.87, 16.21)	9.78 (7.67, 11.89)	19.31 (16.89, 21.73)	14.42 (13.02, 15.82)
Mean fasting glucose[a]	93.01 (92.55, 93.48)	91.22 (90.63, 91.81)	94.19 (93.60, 94.79)	92.97 (92.60, 93.34)
% Low HDL[a]	15.85 (13.87, 17.83)	8.96 (7.05, 10.86)	15.07 (13.05, 17.10)	14.63 (13.22, 16.04)
% Elevated fasting triglycerides	23.08 (20.72, 25.45)	8.99 (7.42, 10.57)	24.89 (22.52, 27.26)	21.27 (19.62, 22.92)
Mean HbA1C[b]	5.12 (5.11, 5.14)	5.26 (5.23, 5.29)	5.17 (5.15, 5.19)	5.15 (5.14, 5.17)

[a]Weighted percentage; 95% confidence interval.
[b]Weighted mean; 95% confidence interval.
BMI, body mass index; ALT, alanine aminotransferase; HDL, high-density lipoprotein; BP, blood pressure; MetS, metabolic syndrome; HbA1C, glycosylated hemoglobin.

30 U/L. In contrast, 842 individuals (16.25%) had elevated ALT levels as defined by the gender-specific cutoffs.

ALT and MetS severity Z-score, BMI Z-score

While there appeared to be a gradual increase in ALT over time, this increase was nonsignificant ($P = 0.08$) (Fig. 1A). There was no change in prevalence of an elevated ALT over time, assessed as odds of higher prevalence in 2013–2014 compared to 1999–2000; this was true using both the cut-off of 30 U/L [OR: 1.05, confidence interval (CI): 0.99–1.12) (Fig. 1D) and the gender-specific cutoff values (OR: 1.04, CI: 0.99–1.10).

To assess for potential influences on the prevalence of elevated ALT, we next evaluated the correlation of BMI and MetS-Z with ALT levels. ALT was significantly correlated with MetS-Z ($r = 0.35$, $P < 0.0001$) (Fig. 2A) and BMI-Z ($r = 0.29$, $P < 0.0001$) (Fig. 2B) (Table 2). This relationship appeared to differ by sex and race/ethnicity, seen by a three-way interaction between MetS-Z, race/ethnicity, and gender. Correlations were evaluated by race and gender and remained significant in each subgroup (all $P < 0.0001$) (Table 2). Non-Hispanic blacks had generally lower correlations between ALT and MetS-Z and BMI-Z, when compared to non-Hispanic whites and Hispanics. Males in each racial/ethnic group appeared to have stronger correlations between ALT

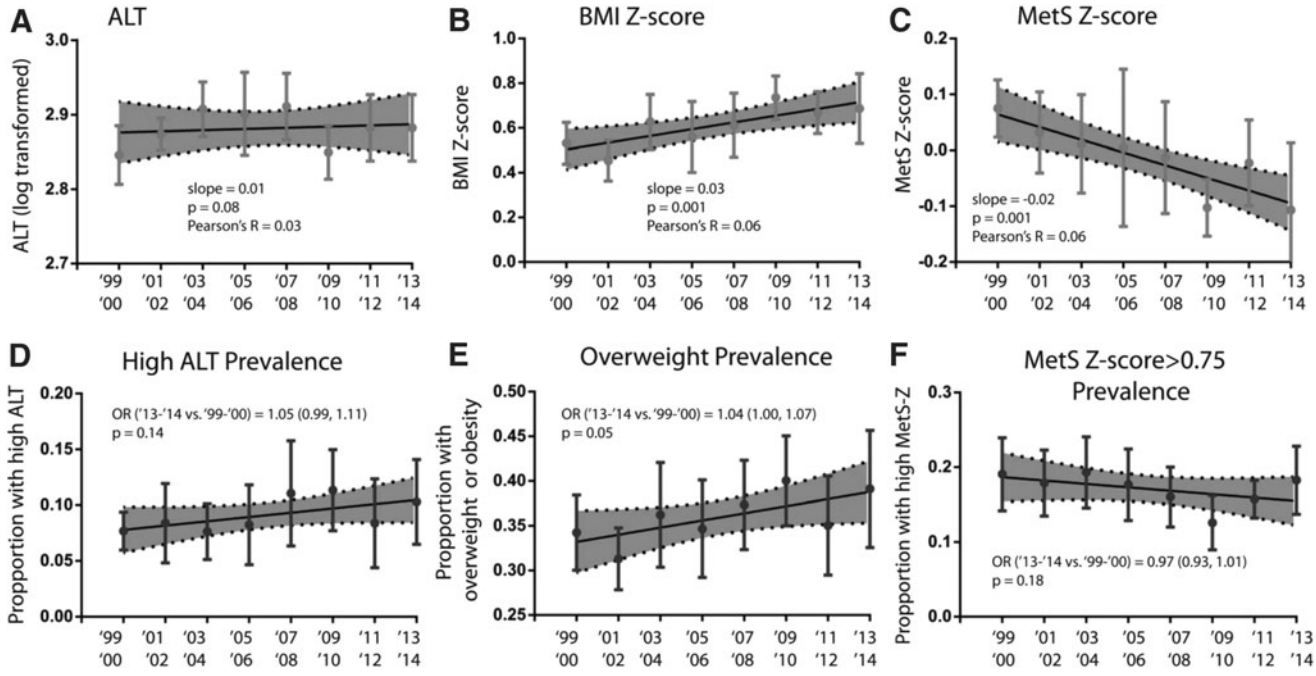

FIG. 1. ALT, BMI-z and MetS severity over time. Data shown reflect mean levels of **(A)** ALT, **(B)** BMI Z-score, and **(C)** MetS Z-score and proportion of adolescents with elevated of **(D)** ALT, **(E)** BMI, and **(F)** MetS Z by NHANES wave weighted to be nationally representative. In **(D–F)**, the odds ratio for the abnormality are provided for last wave vs. first wave. BMI, body mass index; ALT, alanine aminotransferase; MetS, metabolic syndrome.

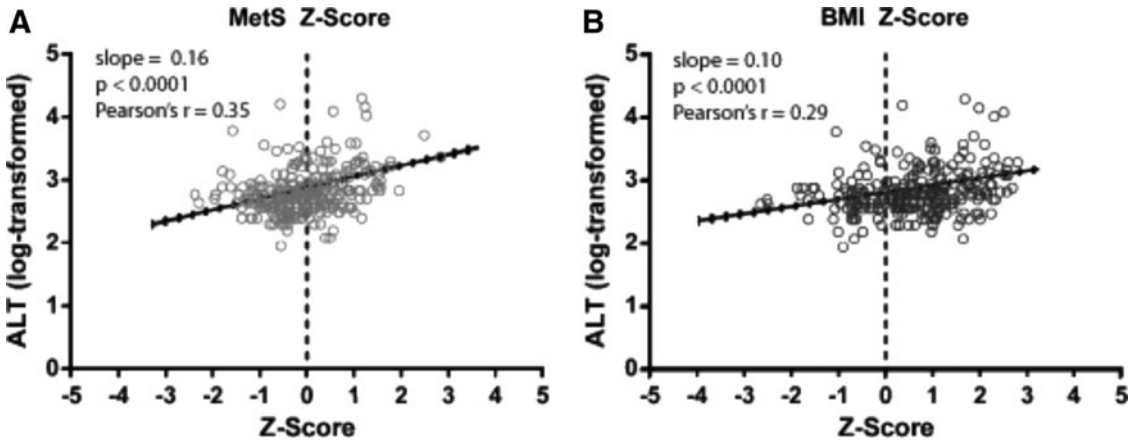

FIG. 2. Linear regression of ALT (log-transformed) with **(A)** MetS Z score and **(B)** BMI Z score.

and MetS-Z/BMI-Z than females. There were significant correlations between ALT and Z-scores of the individual components of MetS, which included blood pressure, fasting triglycerides, fasting glucose, and HDL (Supplementary Table S1).

In addition, the odds of having ALT levels over 30 U/L were significantly heightened in the presence of either elevated MetS-Z (Z-Score >0.75) or BMI >85th percentile (*i.e.*, overweight) with respective OR of 6.99 and 7.04 (Table 3). Using categories of both elevated MetS-Z and overweight BMI, odds of having elevated ALT were highest in non-Hispanic whites, followed by Hispanic participants and non-Hispanic blacks. Similar findings were found when using gender-specific cutoffs (Table 3). These findings did not change after adjustment for total calorie and saturated fat intake, variables available in NHANES that we found to be associated with ALT (results not shown).

Laboratory values and prevalence of elevated ALT over time

Having established links between ALT and BMI and MetS, we assessed for changes in BMI and MetS over time to evaluate whether these trends may have related to a lack of change in ALT. The mean BMI Z-score increased over time ($P = 0.0011$) (Fig. 1B) and the mean MetS Z-score decreased over time ($P = 0.0013$) (Fig. 1C) as reported previously for a different NHANES sample of U.S. adolescents.[25] There was a statistically significant increase in the prevalence of elevated BMI-Z from the 1999–2000 to the 2013–2014 NHANES cycles (OR: 1.04, CI: 1.0–1.07) (Fig. 1E); when stratified by race/ethnicity, only Hispanic adolescents displayed this increasing trend over time (OR 1.05, CI: 1.01–1.09). The prevalence of elevated MetS-Z did not differ significantly over time (OR: 0.97, CI: 0.92–1.02) (Fig. 1F).

TABLE 2. LINEAR REGRESSION OF LOG-ALANINE AMINOTRANSFERASE (AS THE OUTCOME), MODELING SEPARATELY AS A FUNCTION OF METABOLIC SYNDROME-Z AND BODY MASS INDEX-Z (AS PREDICTORS), OVERALL AND BY RACE/ETHNICITY AND GENDER

	Predictor: MetS-Z			*Predictor: BMI-Z*	
	n	*Slope estimate (CI)*	r	*Slope estimate (CI)*	r
All					
Overall	5019	0.16 (0.14–0.18)*,[a]	0.35	0.10 (0.09–0.12)*,[a]	0.29
Males	2635	0.18 (0.15–0.20)*	0.37	0.13 (0.11–0.15)*	0.37
Females	2384	0.10 (0.07–0.12)*	0.24	0.07 (0.05–0.08)*	0.22
NHW					
Overall	1472	0.16 (0.13–0.19)*	0.36	0.10 (0.08–0.12)*	0.30
Males	781	0.17 (0.13–0.21)*	0.38	0.12 (0.10–0.15)*	0.37
Females	691	0.08 (0.04–0.12)*	0.02	0.07 (0.04–0.09)*	0.22
NHB					
Overall	1532	0.11 (0.08–0.14)*	0.25	0.08 (0.06–0.10)*	0.24
Males	844	0.16 (0.12–0.19)*	0.35	0.12 (0.10–0.15)*	0.40
Females	688	0.08 (0.04–0.12)*	0.21	0.05 (0.02–0.07)*	0.17
Hispanic					
Overall	2015	0.20 (0.16–0.23)*	0.37	0.13 (0.11–0.15)*	0.32
Males	1010	0.21 (0.16–0.25)*	0.37	0.15 (0.12–0.18)*	0.38
Females	1005	0.15 (0.11–0.20)*	0.34	0.10 (0.07–0.13)*	0.29

[a]Significant interactions between MetS-Z/BMI-Z and race and gender.
*$P < 0.001$.
CI, confidence interval; NHW, non-Hispanic white; NHB, non-Hispanic black.

Table 3. Odds Ratios (95% Confidence Interval) of Having High Alanine Aminotransferase Measures (Using Two Different Cutoffs), for High Metabolic Syndrome-Z (>0.75 vs. ≤0.75) and High Body Mass Index Percentile (>85th vs. ≤85th), Adjusted for Age and Sex

	Elevated ALT (30 U/L cutoff)		*Elevated ALT gender-specific cutoff (Girls 22 U/L, Boys 25 U/L)*	
	MetS-Z > 0.75	*BMI percentile > 85th*	*MetS-Z > 0.75*	*BMI percentile > 85th*
Overall	6.99 (5.00–9.77)	7.04 (5.40–9.16)	5.67 (4.4–7.3)	4.62 (3.62–5.91)
Non-Hispanic white	7.77 (4.61–13.09)	9.43 (6.17–14.41)	6.31 (4.30–9.25)	5.54 (3.89–7.87)
Non-Hispanic black	5.13 (2.76–9.52)	3.87 (2.10–7.17)	4.66 (3.21–6.76)	3.28 (2.20–4.90)
Hispanic	5.52 (3.81–8.00)	4.83 (3.31–7.04)	4.62 (3.38–6.30)	3.70 (2.76–4.96)

Discussion

Our data demonstrated that there was no significant linear increase in prevalence of elevated ALT using two different cutoffs in U.S. adolescents over a recent 16-year time frame. This was in some ways surprising, given that, (1) there were higher odds of having elevated ALT in the presence of an overweight BMI (or elevated MetS-Z) as noted previously[7,36,37] and (2) the prevalence of overweight in this sample increased over this time frame.[25] While not certain, the reason that ALT elevations did not parallel BMI Z-score elevations may have been because of declining MetS severity Z-score over time. Regardless of the cause, we found the lack of increase in elevated ALT reassuring in the setting of the current obesity epidemic.

In assessing the odds of elevated ALT (>30 U/L) in relationship to BMI Z-score and MetS Z-score, we found higher odds if elevated MetS-Z was present (OR 3.52), compared to if elevated BMI was present (OR 2.789); similar findings were found with the gender-specific cutoffs. There is already a common consensus that NAFLD is associated with MetS components,[1,4] as well as with chronic diseases associated with MetS, like T2DM, cardiovascular disease, and cardiometabolic abnormalities.[1,3,23] Moreover, the dangerous consequences of uncontrolled NAFLD, which include cirrhosis and hepatocellular carcinoma, warrant its early detection and prevention in adolescents.[1–3] While BMI has clear merit as an indicator of risk for elevated ALT levels, the MetS severity Z-score in adolescents may have value as a novel tool for identifying patients with risk of NAFLD as well.

The relationship between ALT and MetS raises the question of what led to this trend of declining MetS during this time period in U.S. adolescents. In a prior analysis, this appeared to be due to improvements in lipid abnormalities related to changes in dietary practices during this time period.[25] Prior work with a different sample of NHANES adolescents showed that adolescents in this time period engaged in healthier food consumption, including a decrease in consumption of total calorie and carbohydrate consumption, as well as an increase in unsaturated fat consumption.[25] During the time frame of this study, there was also an increased push for reduced consumption of unhealthy beverages through efforts like the Dietary Guidelines of America.[38] Between 2001 and 2010, an NHANES analysis found a significant decrease in the purchase and consumption of sugar-sweetened soda, whole milk, fruit juice with sugar added, and fruit-flavored drinks.[39,40] There was also an increased consumption of healthier drink options, including unsweetened juices and lowfat/nonfat milk.[40] Overall, these dietary changes may have contributed to both less MetS and less NAFLD. However, adjustments for diet did not alter our observed associations between MetS and elevated ALT.

In studying the relationship between ALT and MetS and BMI, we found differences that appeared to depend on race/ethnicity and gender. Previous research highlighted similar trends of decreased high ALT prevalence or decreased association with cardiometabolic abnormalities in non-Hispanic blacks, similar to what we found in our analyses.[22,37,41] This appears to support a racial difference in ALT levels and the impact of race/ethnicity on measures of obesity and the MetS. Furthermore, other studies have found no difference among races regarding the upper limit normal ALT level.[36] So, while non-Hispanic black adolescents appear to have a lesser tendency toward cardiometabolism-related ALT abnormalities, it is still sound clinical advice to screen all obese children for elevated ALT, to provide necessary interventions against fatty liver disease. Regarding gender differences, males appear to have stronger correlations than females for MetS-Z and BMI, generally seen in each racial/ethnic group. This finding is in concordance with established evidence of males having an increased prevalence of fatty liver diseases.[5] This also underscores the potential for a gender-specific ALT cutoff to more accurately identify youth at risk for fatty liver.[19]

The gender-specific cutoffs identify almost twice more adolescents with an elevated ALT. Other studies have shown that ALT values lower than the clinically accepted cutoff of 30 U/L can predict fatty liver disease and identification of NAFLD has a gender-related component.[42] Re-evaluation of ALT cutoffs and appropriate screening is needed to accurately identify more individuals at risk of chronic liver diseases, especially if lower cutoffs have better sensitivity without compromising the specificity of the screening tool.[8,19] ALT levels have been found to decrease with healthier diets;[43] so, with earlier identification and intervention, more children may avoid a diagnosis of NAFLD.

This study had several limitations. Because NHANES data were gathered through a cross-sectional study, we are unable to determine causality in the relationships we have described. We lacked consideration of other potentially important factors, including, physical activity, sedentary behavior, and living settings (*e.g.*, rural vs. urban). Furthermore, for the current analyses, we did not focus primarily on factors such as food intake, which have clear importance in the etiology of NAFLD, but are limited in the quality of assessment in large-scale surveys such as this.[44,45]

However, our sensitivity analysis after adjustment for relevant dietary variables revealed our observed associations between MetS and elevated ALT remained. In the future, more work can be done to understand the mechanism behind obesity, MetS, and their potentially causal effects on ALT levels. This study is also limited in the relatively small sample size, due to limitations of fasting status and individuals with missing primary components of the analysis. However, the fasting weights of the complex survey design enabled us to evaluate these as a nationally representative sample. With regard to exclusion criteria, there may be other factors besides diabetes, pregnancy, or Hepatitis B infection that could account for increases in ALT in this population; however, we believe additional excluded participants were a small portion of our sample and would not significantly affect our results. We assessed relationships between multiple variables, raising the potential for identifying associations based on chance alone (*i.e.*, Type 1 error). Finally, there is still some uncertainty if ALT is the best marker for fatty liver disease, since it does not work as a measure of NAFLD severity and may even be normal in individuals with fatty liver disease.[10,12] Given the current markers available for fatty liver disease and the invasive nature of the current gold standard, liver biopsy, ALT still appears to be a useful clinical marker to screen for disease.

Conclusion

We did not observe a statistically significant linear increase in elevated ALT among U.S. adolescents between 1999 and 2014. This finding is potentially related to the divergent effects of worsening obesity and improving MetS in this population. The MetS severity Z-score may be a tool helpful in identifying youth with high ALT levels and possible NAFLD. Continued improvement of diet in this population is advised to improve obesity and related cardiometabolic problems.

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Author Disclosure Statement

No conflicting financial interests exist.

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