 Ethnic Differences in the Link Between Insulin Resistance and Elevated ALT

WHAT’S KNOWN ON THIS SUBJECT: Evaluating for elevations in alanine aminotransferase (ALT) is a common screening test for the presence of nonalcoholic fatty liver disease (NAFLD). NAFLD is less common among non-Hispanic blacks. Better predictors of NAFLD are needed to identify individuals in most need of screening.

WHAT THIS STUDY ADDS: Relative to other ethnicities, metabolic syndrome and insulin resistance performed poorly at identifying non-Hispanic black adolescents with ALT elevations. The presence of metabolic syndrome may therefore not be an adequate trigger for NAFLD screening. Triglyceride elevations performed similarly between groups in identifying ALT elevations.

abstract

BACKGROUND: Nonalcoholic fatty liver disease (NAFLD) exhibits tight links with insulin resistance (IR) and the metabolic syndrome (MetS), a cluster of cardiovascular risk factors. Compared with non-Hispanic whites, non-Hispanic black adolescents have more IR but a lower prevalence of NAFLD and MetS. Our hypothesis was that IR would be a better predictor of alanine aminotransferase (ALT) elevations than is MetS among non-Hispanic blacks.

METHODS: We analyzed data from 4124 adolescents aged 12 to 19 years in the 1999 to 2010 NHANES, using unexplained elevations in ALT (>30 U/L) to characterize presumed NAFLD and using a pediatric adaptation of the Adult Treatment Panel III definition of MetS.

RESULTS: Prevalence of elevated ALT varied by race/ethnicity (Hispanics 13.7%, non-Hispanic white 8.8%, non-Hispanic blacks 5.4%, P < .0001). Among non-Hispanic whites and Hispanics, a classification of MetS performed well in identifying adolescents with elevated ALT (odds ratios [ORs] 9.53 and 5.56, respectively), as did MetS-related indices. However, among non-Hispanic blacks, the association between MetS and ALT elevations was smaller in magnitude and technically nonsignificant (OR = 3.24, P = .051). Furthermore, among non-Hispanic blacks, the presence of IR and elevated waist circumference performed more poorly at identifying ALT elevations (ORs 3.93 and 2.28, respectively) significantly smaller than ORs for non-Hispanic whites, P < .05, with triglyceride elevations being a better predictor (OR = 4.44).

CONCLUSIONS: Non-Hispanic black adolescents exhibit a lower relationship between IR and elevated ALT, supporting racial/ethnic differences in the link between MetS and NAFLD. These data may have implications regarding triggers for screening for NAFLD among non-Hispanic black adolescents, focusing particularly on those with triglyceride elevations. Pediatrics 2013;132:e718–e726

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KEY WORDS
metabolic syndrome, visceral obesity, inflammation, racial/ethnic difference

ABBREVIATIONS
ALT—alanine aminotransferase
BP—blood pressure
GOT—γ-glutamyl transferase
HDL—high-density lipoprotein cholesterol
HOMA-IR—homeostasis model of insulin resistance
hsCRP—high-sensitivity C-reactive protein
IR—insulin resistance
MetS—metabolic syndrome
NAFLD—nonalcoholic fatty liver disease
OR—odds ratio
WC—waist circumference

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Pediatric nonalcoholic fatty liver disease (NAFLD) is a spectrum of liver tissue abnormalities involving hepatic fatty infiltration, ranging from simple steatosis to hepatitis to end-stage liver disease.\textsuperscript{1,2} Inflammation and cellular injury are often indicated by elevations in liver enzymes, particularly alanine aminotransferase (ALT).\textsuperscript{3–5} Pediatric NAFLD has evolved into a serious public health issue, affecting between 7% to 17% of adolescents.\textsuperscript{6,7} Although treatments are limited, lifestyle interventions and weight loss appear beneficial.\textsuperscript{8–10} Long-term prognosis without intervention is variable, but many children may ultimately progress to nonalcoholic steatohepatitis or cirrhosis in childhood or young adulthood.\textsuperscript{11,12} Because the diagnosis of NAFLD involves an invasive procedure (liver biopsy) for its diagnosis, alternative markers have been identified for the presence of NAFLD, of which ALT is the best marker.\textsuperscript{5,7,18} Although elevations in ALT are in no way diagnostic of the presence of NAFLD, elevated ALT in 1 study had a sensitivity of 0.92 for identifying fatty-fibrotic findings on ultrasound.\textsuperscript{14} NAFLD is tightly linked to obesity. Obese children have a sevenfold higher prevalence of NAFLD compared with normal-weight children.\textsuperscript{6} NAFLD is also independently linked to metabolic syndrome (MetS), a cluster of clinical signs and symptoms associated with insulin resistance (IR), including dyslipidemia (elevated triglycerides, low high-density lipoprotein cholesterol [HDL-C]), elevated blood pressure (BP), central/abdominal obesity, and elevated fasting glucose.\textsuperscript{15–17} Obese adolescents with MetS have a fivefold increase in NAFLD compared with obese adolescents without MetS.\textsuperscript{17} The link between NAFLD and IR has raised speculation regarding interrelationships between NAFLD and IR, with shared features of visceral obesity (frequently assessed as elevations in waist circumference [WC]).\textsuperscript{18} Elevated triglycerides, and underlying inflammation, indicated by increases in high-sensitivity C-reactive protein (hsCRP),\textsuperscript{19–21} and γ-glutamyl transferase (GGT),\textsuperscript{22,23} The tight link between MetS and NAFLD has prompted some to suggest screening for NAFLD (via assessment for unexplained ALT elevations >30 U/L) among adolescents with MetS.\textsuperscript{17} However, racial/ethnic discrepancies in MetS may affect its relationship to NAFLD. Non-Hispanic black adolescents have a lower prevalence of MetS\textsuperscript{24–27} and NAFLD\textsuperscript{5,18,28–30} despite having more IR.\textsuperscript{26,31–35} Conversely, Hispanics have a higher prevalence of NAFLD despite similar rates of MetS.\textsuperscript{5,7,13,18,24,25} Given these intergroup differences, our goal was to assess relationships among MetS, IR, and NAFLD between racial/ethnic groups. We evaluated adolescents from the NHANES for unexplained elevations in ALT as a potential marker for NAFLD. Our hypothesis was that given the poor accuracy of MetS for identifying IR in non-Hispanic blacks, MetS would be an overall poor predictor of unexplained ALT elevations among non-Hispanic blacks. We also hypothesized that IR itself would be a better predictor of elevated ALT among non-Hispanic black adolescents. Such data regarding interethnic differences may lead to insights into the underlying processes linking NAFLD and IR.

**METHODS**

Data were obtained from NHANES (1999–2010), a multistage probability sample of the US population. These cross-sectional surveys are conducted by the National Center for Health Statistics of the Centers for Disease Control, with randomly selected subjects undergoing anthropometric and BP measurements, answering questionnaires, and undergoing phlebotomy (http://www.cdc.gov/nchs/nhanes.htm). The National Center for Health Statistics ethics review board reviewed and approved the survey, and participants gave informed consent before participation. Measurement of weight, height, BMI, WC, BP, and laboratory measures of ALT, aspartate aminotransferase, GGT, hsCRP, triglycerides, HDL-C, and glucose were obtained by using standardized protocols and calibrated equipment.\textsuperscript{36–38} Only blood samples obtained after an ≥8-hour fast were analyzed. Participants were classified as overweight if their BMI z score was in the 85th to 95th percentile for age and obese if their BMI z score was ≥95th percentile. We excluded individuals with positive serologic studies associated with viral hepatitis, including those with a positive hepatitis B core antibody, hepatitis B surface antigen, hepatitis C confirmed antibody, and hepatitis D antibody. Subjects were also excluded if they were pregnant, had known diabetes, or were taking antidiabetic or anti-hyperlipidemic medications because these situations are all likely to alter lipid and insulin levels in a manner that may not reflect baseline insulin-NAFLD correlations. Individuals taking antihypertensive medication were classified as having hypertension. Data were not readily available regarding alcohol intake in this age range.

**Outcome Variable: ALT**

We used an upper limit value for ALT of 30 U/L, derived as the 97th percentile from NHANES III\textsuperscript{37} and used previously.\textsuperscript{7} Data from non-Hispanic white, non-Hispanic black, or Hispanic (Mexican-American/other Hispanic) adolescents, aged 12 to 19 years were analyzed. Children <12 years were excluded because fasting laboratory values were only obtained in participants ≥12 years.

**MetS Classification**

MetS was defined by a commonly used pediatric/adolescent adaptation of the Adult Treatment Panel III criteria.\textsuperscript{26}
Participants had to meet ≥3 of the following 5 criteria: (1) concentration of triglycerides ≥110 mg/dL; (2) HDL-C ≤40 mg/dL; (3) WC ≥90th percentile for age/gender (or Adult Treatment Panel III limit of 102 cm for males and 88 cm for females, whichever was lower); (4) glucose concentration ≥100 mg/dL; and (5) systolic or diastolic BP ≥90th percentile (age, height, and gender-specific). Hypertension was defined as systolic or diastolic BP ≥90th percentile for age, height, and gender. The homeostasis model of IR (HOMA-IR) was calculated as [(fasting insulin in mU/mL) × fasting glucose in mg/dL/405]. IR was defined as HOMA-IR ≥4.0 as done previously in adolescents.40

Statistical Analysis
Statistical significance was defined as a P < .05. Statistical analysis was performed using SAS (version 9.3, Cary, NC), using survey procedures (eg, SURVEYREG) that account for the survey design when estimating SEs to obtain population-based estimates. We combined data sets from the six 2-year cycles (1999–2010) for statistical analyses to increase sample size. Prevalence rates of MetS, NAFLD (classified as ALT ≥30), and elevated HOMA (≥4.0) were calculated by gender and race/ethnicity and compared via χ² tests. Mean levels of relevant continuous measures were compared among groups by using either t tests or analysis of variance. Various regression models were fit to the data, all including gender, ethnicity (highest level obtained for any household member), and household income-to-needs ratio as covariates. Logistic regression was used to assess effects of gender, race/ethnicity, and MetS status on the odds of NAFLD. All interactions of the 3 covariates (gender, race/ethnicity, and MetS status) were initially included in the model but removed in a stepwise fashion if the associated interaction P value was >.10. Separate logistic models of NAFLD were also fit to the data, examining the impact of MetS, MetS components, and other elevations (HOMA-IR, hsCRP) on the odds of NAFLD by race/ethnicity. Odds ratios (ORs) adjusting for the aforementioned covariates were estimated to compare odds of NAFLD for increasing numbers of MetS elevations. Linear regression was used to compare mean levels of triglycerides, hsCRP, and GGT between those with ALT ≥30 versus <30. Comparisons between the 2 ALT groups were allowed to vary by race/ethnicity. We stratified subjects by age (boys ≥16 years and girls ≥14 years) to assess for differences in these findings among children likely to be in later pubertal stages.41,42 Natural log transformations were used to achieve normality; geometric means from these models were reported. Finally, OR of ALT elevations were estimated comparing quartiles of various MetS or MetS-related measures.

RESULTS
Prevalence of MetS and Unexplained ALT Elevations
We evaluated 4124 adolescents, including 1207 non-Hispanic whites, 1233 non-Hispanic blacks, and 1684 Hispanics. The prevalence of abnormal ALT levels in adolescents differed by race/ethnicity. Hispanics, 13.7%; non-Hispanic whites, 8.6%; and non-Hispanic blacks, 5.4% (P < .0001; Table 1). Similarly, the prevalence of MetS also differed by race/ethnicity: Hispanics, 10.6%; non-Hispanic whites, 8.4%; and non-Hispanic blacks, 4.2%. Both elevated ALT levels and MetS were more common among overweight and obese adolescents than normal-weight adolescents for each racial/ethnic group (Supplemental Table 5). IR defined as HOMA-IR ≥4.040 was higher in non-Hispanic blacks and Hispanics compared with non-Hispanic whites (Table 1). These findings were similar when fasting insulin was evaluated (data not shown). Mean values for MetS components, insulin, ALT and aspartate aminotransferase, and inflammatory markers are shown by gender and race/ethnicity in Supplemental Table 6. Values differed significantly by race/ethnicity for multiple variables. Non-Hispanic blacks had the highest values of high-density lipoprotein, systolic BP, and GGT, and the lowest values of glucose, triglycerides, and ALT.

OR of Elevated ALT
In a model adjusting for household education and income, the factors associated with risk of ALT elevation included male gender (OR = 4.59, 95% CI = 3.24–6.49, P < .0001), Hispanic ethnicity (OR = 1.8, 95% CI = 1.24–2.61, P < .01), and MetS (OR = 7.81, 95% CI = 5.24–11.65, P < .0001; Table 2). Notably, there was no significant interaction between gender, race/ethnicity, and MetS in their relationship to elevated ALT, suggesting that MetS correlated similarly between males and females (and among race/ethnic groups) in its relationship to NAFLD. Even though the race/ethnicity × MetS interaction was not significant (P = .22), we kept this interaction in the next set of models to allow for the impact of MetS (and its components in separate models each) on the odds of ALT elevation to vary by race/ethnicity (Table 3). Here, MetS was a significant predictor of ALT elevations among non-Hispanic white (OR = 9.53, 95% CI = 5.58–16.27, P < .0001) and Hispanic (OR = 5.56, 95% CI = 3.10–9.95, P < .0001) adolescents. Among non-Hispanic blacks, the relationship between MetS and elevated ALT was lower in magnitude and not technically significant (OR 3.24, 0.99–10.54, P = .0514; Table 3). Abnormalities in individual MetS
TABLE 1 NHANES 1999–2010 Characteristics: Children Aged 12 to 19 Years With Data on All MetS Components (n = 4124)

<table>
<thead>
<tr>
<th></th>
<th>% With Elevated ALT (95% CI)</th>
<th>% With MetSb (95% CI)</th>
<th>% With IRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>4124</td>
<td>9.0 (7.5–10.5)</td>
<td>8.1 (6.8–9.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.0 (14.4–17.5)</td>
<td></td>
</tr>
<tr>
<td>By gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1946</td>
<td>3.3 (2.4–4.2)</td>
<td>5.3 (4.1–6.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.8 (13.5–18.1)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2178</td>
<td>14.4 (11.8–17.1)</td>
<td>10.9 (8.7–13.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16.1 (13.7–18.5)</td>
<td></td>
</tr>
<tr>
<td>P*</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>.8879</td>
</tr>
<tr>
<td>By race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1207</td>
<td>8.6 (6.6–10.5)</td>
<td>8.4 (6.5–10.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.9 (10.8–15.0)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>1233</td>
<td>5.4 (3.5–7.3)</td>
<td>4.2 (2.9–5.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19.4 (17.1–21.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>1684</td>
<td>13.7 (11.5–15.8)</td>
<td>10.6 (8.4–12.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24.3 (21.2–27.4)</td>
<td></td>
</tr>
<tr>
<td>P*</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

CI, confidence interval.
* ALT ≥50.
b Pediatric Adaptation of Adult Treatment Panel III of Metabolic Syndrome.
† HOMA-IR ≥4.0.
‡ χ² test comparing rates among the race/ethnicity groups.
§ χ² test comparing rates between males and females.

TABLE 2 Logistic Model of Odds of ALT ≥30

<table>
<thead>
<tr>
<th>Model Covariate</th>
<th>OR Estimate</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>0.93</td>
<td>(0.55–1.58)</td>
<td>.8002</td>
</tr>
<tr>
<td>High school</td>
<td>0.95</td>
<td>(0.53–1.71)</td>
<td>.8712</td>
</tr>
<tr>
<td>More than high school</td>
<td>1 (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household income</td>
<td>0.99</td>
<td>(0.87–1.11)</td>
<td>.8285</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4.59</td>
<td>(3.24–6.49)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Female</td>
<td>1 (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>0.74</td>
<td>(0.48–1.13)</td>
<td>.1648</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.80</td>
<td>(1.24–2.81)</td>
<td>.0022</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>1 (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MetS</td>
<td>7.81</td>
<td>(5.24–11.65)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

All interactions among race/ethnicity, gender, and MetS were not significant (P > .20) and were removed from the model. 
CI, confidence interval.

TABLE 3 Adjusted ORs of ALT ≥30 by Race/Ethnicity

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hispanic White</td>
</tr>
<tr>
<td>MetS components</td>
</tr>
<tr>
<td>Elevated WC</td>
</tr>
<tr>
<td>Elevated BP</td>
</tr>
<tr>
<td>Low HDL-C</td>
</tr>
<tr>
<td>Elevated triglycerides</td>
</tr>
<tr>
<td>Elevated glucose</td>
</tr>
<tr>
<td>Other outcomes</td>
</tr>
<tr>
<td>Elevated HOMA-IR (≥4.0)</td>
</tr>
<tr>
<td>Elevated hsCRP (≥4.5)</td>
</tr>
</tbody>
</table>

Adjusted for gender, household income, and highest household education. CI, confidence interval.
* P < .05 (Comparing OR to Non-Hispanic whites).
** P < .01 (Comparing OR to Non-Hispanic whites).

components, IR, and elevated hsCRP also performed well in general as predictors of ALT elevations. However, elevations in WC and HOMA-IR had significantly lower OR for elevated ALT among non-Hispanic blacks compared with non-Hispanic whites (P = .0044 and P = .0189 for interethnicity comparison, respectively), whereas elevations in triglycerides were the best predictor of ALT elevations among non-Hispanic blacks (Table 3).

Inflammation and Elevated ALT

We next assessed for differences in systemic inflammation among adolescents with and without unexplained ALT elevations by racial/ethnic group, using hsCRP and GGT as inflammatory measures and adjusting for household education and income (Table 4). Geometric means of these measures estimated from the linear models of the log-transformed outcomes were compared between those with and without elevated ALT. Among each racial/ethnic group, there was a higher degree of systemic inflammation among adolescents with ALT elevations. Non-Hispanic black adolescents without ALT elevations had higher mean levels of GGT than non-Hispanic whites, whereas Hispanics had lower hsCRP levels than non-Hispanic whites. Levels of inflammatory markers were otherwise similar by race/ethnicity.

ALT Elevation by HOMA-IR, WC, and Triglyceride Quartiles

Finally, we divided HOMA-IR, triglycerides, and WC into quartiles among the overall sample to assess for increases in the odds of unexplained ALT elevations with increasing degree of these measures while adjusting for gender, household education, and income. Although all racial/ethnic groups exhibited higher adjusted ORs of ALT elevation among individuals in the highest quartile for HOMA-IR compared with the lowest, this OR was significantly lower among non-Hispanic blacks (2.9) compared with non-Hispanic whites (8.5) but not compared with Hispanics (9.6; Fig 1A). The same was true for OR of ALT elevation by quartiles.
of WC, with a lower adjusted OR for elevated ALT among non-Hispanic blacks (4.8) compared with non-Hispanic whites (11.4, 95% CI 11.1–11.8) and Hispanics (16.1, P > .05; Fig 1B). Although lower levels of triglycerides carried low OR of ALT elevation in non-Hispanic black adolescents, non-Hispanic blacks with triglycerides in the top quartile exhibited a similar OR (4.8) to that seen in non-Hispanic whites (4.7). Hispanics with triglycerides in the top quartile had the highest OR of ALT elevations of any of the racial/ethnic groups (10.7, 95% CI 10.4–11.0 versus non-Hispanic whites; Fig 1C). When fasting insulin was substituted for HOMA-IR, this yielded nearly identical results (data not shown). We did not have data regarding pubertal status in this database; however, when we stratified by age group to assess these findings among children likely to be in late puberty (boys aged ≥16 years; girls aged ≥14 years41,42), we found similar findings regarding these interethnicity differences (data not shown).

**DISCUSSION**

Racial/ethnic variation in NAFLD and/or ALT elevations5,7,18,28–30,43,44 and MetS24–27,32–34 have been noted previously, suggesting clear differences in obesity-related changes in fatty liver and IR. Non-Hispanic blacks in particular have a low prevalence of NAFLD5,18 and MetS24–27 despite a high degree of IR. Given known inaccuracies of current MetS criteria in identifying IR and inflammation among non-Hispanic black adolescents, our original hypothesis was that the degree of elevation in HOMA-IR would prove to be better than MetS at predicting elevations in ALT. This was technically true, with a nonsignificant OR for MetS predicting ALT elevations (OR = 3.24, P = .05), compared with a significant OR for elevated insulin (OR = 3.45, 95% CI 3.29–3.61, P < .01), although with a larger sample size statistical correlation may have been noted for both. Nevertheless, what was much more striking was that HOMA-IR did not have as close of an association with ALT elevations among non-Hispanic blacks as among the other ethnicities. Although other reports have shown less NAFLD in non-Hispanic blacks, this report represents the first demonstration of a weaker link between HOMA-IR and ALT elevations as a marker for suspected NAFLD among non-Hispanic blacks. That these findings are present (1) at a relatively early age, (2) in a population largely free from medical comorbidities, and (3) after adjustment for socioeconomic factors supports the presence of clinically significant racial/ethnic differences in hepatic response to obesity and IR.

Notably, non-Hispanic blacks are less likely to have visceral adiposity as assessed by computed tomography51,52 and elevated WC,25 potentially producing a lower propensity toward hepatic fat accumulation.18,46 Non-Hispanic blacks also have a low prevalence of MetS diagnosis, predominantly related to having lower triglyceride levels than other racial/ethnic groups,47 making MetS a poorer marker of IR in non-Hispanic blacks.26,32,35,48 Our present findings build on these assertions by revealing that even in the presence of elevated WC and HOMA-IR, non-Hispanic black adolescents have a lower OR than non-Hispanic whites for suspected NAFLD.

In considering these associations, it is notable that the cause-effect relationship between NAFLD and MetS likely involves some degree of overlap. Clearly the presence of NAFLD is associated with elevated levels of inflammation19,20 and IR17,49,50 and, when present, is likely to contribute to the findings associated with MetS.17 In this sense, previous studies would suggest that NAFLD may be a cause of worsening MetS. Conversely, the underlying processes of obesity, inflammation, and adipokines that drive abnormalities associated with MetS are also associated with NAFLD in basic science models51,52 and may contribute to liver fat accumulation through related pathways.15 In this sense, individuals with a high degree of IR from these processes would be expected to have a higher risk of NAFLD, highlighting how NAFLD may be an effect of processes behind MetS. Nevertheless, both of these cause-effect situations appear diminished among non-Hispanic black adolescents compared with other groups in that the lower prevalence of NAFLD was not associated with lower levels of...
inflammation or IR, and a similar or higher degree of IR in non-Hispanic blacks compared with other groups did not correlate with higher rates of NAFLD. Although the cross-sectional nature of these data limits the conclusions we can make regarding these relationships, these findings overall suggest a lower degree of association among MetS, IR, and NAFLD in non-Hispanic black adolescents compared with non-Hispanic whites and Hispanics, as illustrated by Table 3 and Fig 1A.

These findings may pertain to differences in body fat distribution among non-Hispanic blacks, who notably have less visceral adiposity. Although visceral obesity is tightly linked to IR, this link does not appear necessary in non-Hispanic blacks. However, non-Hispanic blacks have more subcutaneous fat. Basic science studies have suggested that the ability to deposit large quantities of fat in subcutaneous tissue protects against deposition in visceral and hepatic compartments. Nevertheless, we noted that even when WC is elevated in non-Hispanic black adolescents, suggesting increase in visceral adipose tissue, there were lower ORs for suspected NAFLD than seen for non-Hispanic whites (Fig 1B). This would appear to additionally dissociate visceral adiposity from NAFLD in non-Hispanic black adolescents.

The most notable difference in MetS between non-Hispanic blacks and other ethnicities is a lower prevalence of hypertriglyceridemia, which may be due in part to lower activity of lipoprotein lipase. Interestingly, one of the pathophysiologic processes associated with NAFLD is an increase in free fatty acids from the liver, also noted in elevations in triglycerides, which are elevated on average 40% among adolescents with suspected NAFLD compared with control subjects. We noted that despite lower triglyceride levels overall among non-Hispanic blacks, when non-Hispanic black adolescents do have high triglyceride levels, they had a similar OR for elevated ALT as non-Hispanic whites (Fig 1C). Thus, although ALT increases are associated overall with central obesity, low HDL-C, and high triglycerides, it appears that among non-Hispanic black adolescents, high triglycerides constitute a particularly good marker of elevated ALT risk. It is unclear if non-Hispanic blacks with such elevations in triglycerides represent a subgroup with a particularly progressed condition of MetS or if their triglyceride...
Elevations represent differences in genetic propensity to both manifestation of MetS and development of NAFLD. Regardless, suspicion of potential NAFLD among non-Hispanic blacks should rise when elevated triglycerides are present, more so than other features of MetS, potentially representing a new indicator for screening for NAFLD among non-Hispanic blacks.

In contrast to these findings regarding non-Hispanic blacks, our findings support a relationship between IR and NAFLD that is at least as strong, if not stronger, among Hispanics as among non-Hispanic whites. Hispanics have been noted to have more NAFLD with worsened severity and higher rates of nonalcoholic steatohepatitis.\textsuperscript{15,15} Although a lower relationship between IR and NAFLD has been suggested among Hispanics versus non-Hispanic whites in past studies,\textsuperscript{49} other researchers have found that, when matched for the degree of adiposity, Hispanics and non-Hispanic whites exhibited similar relationships between IR and fatty liver disease severity.\textsuperscript{44} Our data support overall similarities in the relationship between IR and NAFLD among Hispanics and non-Hispanic white adolescents, with, if anything, a tendency toward higher OR for NAFLD in Hispanics with fasting insulin and WC in the highest quartile.

Our study had multiple limitations. We used cross-sectional data from NHANES. This permitted analysis of a large US population-based sample of adolescents, but the cross-sectional nature does not permit conclusions on the temporal nature of MetS and NAFLD. Although powerful, the NHANES data we used also do not contain information regarding pubertal status, which is of clear importance in the consideration of IR; however, when we stratified by age to evaluate children more likely to be in late puberty (boys aged \( \geq 16 \) years; girls aged \( \geq 14 \) years\textsuperscript{41,42}) we found similar results, suggesting against a puberty-related cause of these findings. We used unexplained ALT elevations to assess for suspected NAFLD.

Although we excluded individuals with serological findings of hepatitis, there still may have been non-NAFLD causes of these ALT elevations such as hepatitis types not evaluated in NHANES, Wilson's disease, and chronic alcohol use. Nevertheless, use of ALT elevations has been validated in previous studies as a strong predictor of NAFLD in children\textsuperscript{4} and adults\textsuperscript{3} and has been widely used in other epidemiologic studies.\textsuperscript{5,7,13} Finally, we were not able to directly measure IR, instead using HOMA-IR and fasting insulin as measures of IR. Although still an imperfect means of estimating insulin sensitivity, HOMA-IR and fasting insulin overall correlate with the hyperinsulinemic-euglycemic clamp method, the gold standard for assessing IR.\textsuperscript{56}

CONCLUSIONS

We found racial/ethnic differences in the relationship between elevated ALT and IR. The presence of IR and elevated WC were poorer predictors of elevated ALT overall among non-Hispanic blacks compared with non-Hispanic whites and may not be as effective of triggers for screening for NAFLD in non-Hispanic blacks, whereas elevated triglyceride levels may be a better indication for screening among non-Hispanic black adolescents. These data add to accumulating evidence of differences in how MetS and related diseases are manifest in non-Hispanic blacks and may reflect a need for ethnicity-based screening criteria for adolescents at risk for NAFLD. Clearly more research is necessary.

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Ethnic Differences in the Link Between Insulin Resistance and Elevated ALT
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