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Associations of insulin resistance and glycemia with liver enzymes in Hispanic/Latino youths: Results from the Hispanic Community Children’s Health Study/Study of Latino Youth (SOL Youth)

Christina M. Parrinello, PhD, MPH¹, Bryan J. Rudolph, MD², Mariana Lazo, MD, PhD, ScM³, Linda C. Gallo, PhD⁴, Bharat Thyagarajan, MD, PhD⁵, Scott J. Cotler, MD⁶, Qibin Qi, PhD¹, Tossaporn Seeherunvong, MD⁷, Denise C. Vidot, PhD⁸, Howard D. Strickler, MD, MPH¹, Robert C. Kaplan, PhD¹, and Carmen R. Isasi, MD, PhD¹

¹Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

²Department of Pediatrics, Albert Einstein College of Medicine, Bronx, NY, USA

³Johns Hopkins School of Medicine and the Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD, USA

⁴Department of Psychology, San Diego State University, San Diego, CA, USA

⁵Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, MN, USA

⁶The Program for Experimental and Theoretical Modeling, Division of Hepatology, Department of Medicine, Loyola University Chicago, Medical Center, Maywood, IL, USA

⁷Division of Pediatric Endocrinology, University of Miami Leonard M. Miller School of Medicine, Miami, FL, USA

⁸Department of Psychology, University of Miami, Coral Gables, FL, USA

Abstract

Background—Associations of insulin resistance and hyperglycemia with a panel of liver enzymes have not been well-studied in a young, heterogeneous Hispanic/Latino population. We aimed to assess the associations of insulin resistance and glycemia with nonalcoholic fatty liver disease (NAFLD), as measured by liver enzymes and the pediatric NAFLD fibrosis index (PNFI), and whether these associations are modified by body mass index and mediated by inflammation or endothelial dysfunction.

Corresponding author: Carmen R. Isasi, MD, PhD, 1300 Morris Park Avenue, Belfer 1308D, Bronx, NY 10461, 718-430-2950, carmen.isasi@einstein.yu.edu.

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Author contributions: CMP: designed the study, conducted the analysis, interpreted the data, and drafted the manuscript; BJR, ML, LCG, BT, SJC, QQ, TS, DCV, HDS, and RCK: interpreted the data and critically revised the manuscript; and CRI: designed the study, acquired the data, interpreted the data, and critically revised the manuscript. All authors gave final approval of the version to be submitted for publication and agreed to be accountable for all aspects of the work.

Methods—We conducted a cross-sectional study of 1,317 boys and girls aged 8–16 years from the Hispanic Community Children’s Health Study/Study of Latino Youth. We used Poisson regression to assess the associations of fasting glucose, HbA1c, and HOMA-IR with elevated ALT (>25 U/L in boys, >22 U/L in girls), AST (>37 U/L), GGT (>17 U/L), and PNFI (>9; a function of age, waist circumference, and triglyceride level).

Results—HOMA-IR was associated with elevated ALT, AST, GGT, and PNFI (prevalence ratios [95% CIs] for each 1-unit increase in the natural log of HOMA-IR: 1.99 [1.40, 2.81], 2.15 [1.12, 4.12], 1.70 [1.26, 2.30], and 1.98 [1.43, 2.74], respectively). Associations were observed in overweight/obese children, but not in normal weight children (p-interaction=0.04 for AST and p-interaction=0.07 for GGT). After further adjustment for adiponectin, high-sensitivity C-reactive protein, e-selectin, and PAI-1, associations of HOMA-IR with liver enzymes and PNFI were attenuated, but remained statistically significant for AST and PNFI.

Conclusion—Insulin resistance was associated with NAFLD in overweight/obese Hispanic/Latino youth, and this association may be partially mediated by inflammation and endothelial dysfunction.

Keywords

NAFLD; insulin resistance; adolescents; glycemia; Hispanic

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of pediatric liver disease in the United States.^{1,2} It is characterized by fat accumulation in the liver that can progress to liver inflammation (nonalcoholic steatohepatitis [NASH]) and then fibrosis.¹ Biopsy is the gold standard for identifying and staging NAFLD, but is an invasive procedure and an impractical population-level screening test. It is therefore only selectively used in adults and is even more limited in use among children. Whereas ultrasound and other scanning methods (e.g., transient elastography) are often used in evaluating NAFLD, liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and gamma-glutamyl transpeptidase [GGT]) are also used clinically and in research studies as noninvasive surrogate markers of liver injury and likelihood of NAFLD and fibrosis, along with various noninvasive indices of liver fibrosis such as the pediatric NAFLD fibrosis index (PNFI), which is calculated using clinical markers (age, waist circumference, and triglyceride levels).^{3,4}

In adults, higher levels of liver enzymes have been associated cross-sectionally and prospectively with metabolic syndrome, insulin resistance, hyperglycemia, and diabetes.^{5–12} Similar associations have been observed in young children and adolescents.^{13–19} As suggested by these studies, NAFLD could interfere with the insulin signaling pathway and lead to insulin resistance.²⁰ However, the relationship between hyperglycemia/insulin resistance and NAFLD may be bidirectional or even circular.²¹ It is possible that hyperglycemia and insulin resistance could lead to liver injury through various pathways, including increased inflammation and endothelial dysfunction.^{22,23} Whereas both insulin

resistance and NAFLD are clearly influenced by obesity, the mechanisms linking insulin resistance to NAFLD, and vice versa, have not been fully elucidated.

Insulin resistance and NAFLD both have particularly high prevalence among Hispanics/Latinos and among obese males in general.^{24,25} Whereas these studies have predominantly included Hispanic/Latino youth and adults of Mexican heritage, data on Hispanics/Latinos of other backgrounds are lacking. In fact, recent data in adults have shown that the prevalence of diabetes and NAFLD varies by Hispanic/Latino background.^{26,27} Associations of insulin resistance and in particular, hyperglycemia, with a panel of liver enzymes have not been well-studied in a young, heterogeneous Hispanic/Latino population. Given the high prevalence and increasingly early onset of obesity and glucose dysregulation in Hispanic/Latino youth,²⁸ this is an especially important population in which to investigate these relationships. Therefore, we aimed to assess the associations of insulin resistance and glycemia with liver enzymes and PNFI in Hispanic/Latino children and adolescents; and whether these associations are modified by age, sex, or body mass index (BMI), and/or mediated by biomarkers of inflammation and endothelial dysfunction. These objectives were addressed using the diverse Hispanic Community Children's Health Study/Study of Latino Youth (SOL Youth) population aged 8–16 years from various Hispanic/Latino backgrounds.

Materials and Methods

Study population

There were 1,466 boys and girls, aged 8–16 years, recruited into SOL Youth (described previously²⁹) from four US cities.³⁰ Our analytic sample included 1,317 participants. See exclusions in the Online Supplement. The study was approved by institutional review boards at each site. Written informed consent was obtained from parents/legal guardians. Assent was obtained from children.

Laboratory measurements

Morning blood specimens were collected from fasting participants. Measurements included ALT, AST, GGT, fasting glucose, HbA1c, insulin, adiponectin, plasminogen activator inhibitor (PAI)-1, e-selectin, high-sensitivity C-reactive protein (hs-CRP), HDL-c, triglycerides, cholesterol, LDL-c (calculated using the Friedewald equation). We calculated HOMA-IR as $[\text{glucose (in mg/dL)} * [\text{insulin (in pmol/L)}] / 6] / 405$.³¹ See Online Supplement for more details.

Self-reported covariates

The following were reported by the child/adolescent and/or the parent: age, sex, Hispanic/Latino background, household income, parental education attainment, alcohol use in the past 30 days, having experienced menarche (girls), and stage of facial hair growth (boys).³² We created a dichotomous variable for pubertal (having reached menarche for girls and having at least started growing facial hair for boys) or pre-pubertal status.

Measured covariates

Centers for Disease Control age- and sex-specific BMI percentiles,³³ and NHLBI age-, sex-, and height-specific diastolic and systolic blood pressure percentiles were calculated.³⁴ Elevated waist circumference was defined as having an age- and sex-specific waist circumference $\geq 90^{\text{th}}$ percentile.³⁵ We report the number of minutes of moderate/vigorous activity (≥ 441 counts/15 seconds) per day from accelerometers.³⁶ See Online Supplement for additional details.

Variable definitions

We defined elevated biomarker levels as follows: ALT >25 U/L in boys and >22 U/L in girls;³⁷ AST ≥ 37 U/L; GGT ≥ 17 U/L; PNFI ≥ 9 (since suggestive of hepatic fibrosis)⁴; HOMA-IR ≥ 2.6 (insulin resistance);³⁸ and hyperglycemia as either fasting glucose ≥ 100 mg/dL or HbA1c $\geq 5.7\%$.³⁹ We calculated the PNFI as $(1/(1+(\exp(-\text{lp}))))*10$, where $\text{lp} = (-6.539*(\ln(\text{age}))) + (0.207*\text{waist}) + (1.957*(\ln(\text{tg}))) - 10.074$.⁴ BMI was categorized as underweight/normal weight ($<85^{\text{th}}$ percentile), overweight (85^{th} to $<95^{\text{th}}$ percentile), or obese ($\geq 95^{\text{th}}$ percentile).

Statistical analyses

We log-transformed variables that were not normally distributed. We used Wald tests to compare characteristics by level (normal versus elevated) of ALT, AST, GGT, and PNFI. We compared the percentage of participants who had elevated levels of ALT, AST, GGT, PNFI, fasting glucose, HbA1c, or HOMA-IR across categories of age, sex, BMI, Mexican background, and Hispanic/Latino background using a Wald test of joint significance from logistic regression. Supplemental analyses were stratified by sex, pubertal status, and BMI category.

We used Poisson regression with robust variance to assess the association of HOMA-IR, fasting glucose, and HbA1c (as continuous variables) with elevated ALT, AST, GGT, and PNFI. We sequentially adjusted for covariates listed previously. Models for PNFI were not adjusted for age, waist circumference, or triglyceride level since PNFI is a function of those variables. A sensitivity analysis used linear regression with ALT, AST, GGT, and PNFI as continuous variables.

We tested for the interaction of age, sex, Mexican background and BMI (normal weight vs overweight/obese) with HOMA-IR, glucose, and HbA1c using Wald tests. We observed evidence of statistically significant interactions of BMI with HOMA-IR and therefore present the associations of HOMA-IR with ALT, AST, GGT, and PNFI stratified by BMI category. These stratified analyses were not adjusted for BMI percentile or elevated waist circumference, since only one participant in the normal weight category had elevated waist circumference.

Subsequent analyses examined potential mediators of the association between liver function measures and study endpoints by sequentially adjusting for adiponectin, ln of hs-CRP, e-selectin, and ln of PAI-1. See additional details in the Online Supplement. A sensitivity analysis excluded 59 participants who reported alcohol use in the past 30 days.

We used MI ESTIMATE commands in Stata version 14.0 (StataCorp, College Station, Texas, USA) to simultaneously account for the complex survey sampling design and multiple imputation. See Online Supplement.

Results

Among 1,317 participants, mean age was 12.2 years, 51% were male, and 46% were overweight or obese. Participants who were male, overweight/obese, or had elevated waist circumference were more likely to have elevated levels of liver enzymes and PNFI (Table 1). Those with elevated liver enzymes and elevated PNFI were more likely to have lipid abnormalities (higher levels of total cholesterol, LDL-c, and triglycerides, and lower levels of HDL-c), higher levels of inflammation (as measured by higher hs-CRP), lower levels of adiponectin, greater endothelial dysfunction (higher levels of PAI-1 and e-selectin), and more insulin resistance (as measured by higher HOMA-IR) (Table 1).

Boys were more likely than girls to have elevated liver enzymes and hyperglycemia (as measured by fasting glucose and HbA1c), but less likely to have insulin resistance (47% of boys versus 59% of girls) (Table 2). Obese children were more likely to have elevated liver enzymes and PNFI, hyperglycemia, and insulin resistance (Table 2). These results for obesity were similar regardless of pubertal status (eTable 1). Participants of Mexican heritage were more likely to have elevated ALT than those of non-Mexican heritage (Table 2).

Higher levels of HbA1c were associated with elevated ALT and PNFI in minimally adjusted models, but associations were not statistically significant in fully adjusted models (Figure). We did not observe any associations of fasting glucose with elevated liver enzymes and PNFI. Associations of HOMA-IR with elevated liver enzymes and PNFI were statistically significant and remained so after full adjustment (Model 3) (prevalence ratios [95% CIs] were 1.99 [1.40, 2.81], 2.15 [1.12, 4.12], 1.70 [1.26, 2.30], and 1.98 [1.43, 2.74] for ALT, AST, GGT, and PNFI, respectively) (Figure). Sensitivity analyses using liver enzymes and PNFI as continuous variables in linear regression models yielded similar results (eTable 2).

We observed statistically significant interactions between BMI (overweight/obese versus under/normal weight) and HOMA-IR in association with elevated liver enzymes ($P=0.04$ for elevated AST and $P=0.07$ for elevated GGT). In multivariable models that were stratified by BMI category, we found no statistically significant association of HOMA-IR with elevated liver enzymes in under/normal weight children. However, we observed consistent statistically significant associations in those who were overweight or obese (prevalence ratios [95% CIs] were 2.40 [1.61, 3.58], 4.50 [2.14, 9.48], 1.75 [1.34, 2.29], and 3.12 [2.39, 4.05] for elevated ALT, AST, GGT, and PNFI, respectively) (Table 3). Results were attenuated after adjustment for adiponectin, but remained statistically significant. Additional sequential adjustment for ln of hs-CRP, e-selectin, and ln of PAI-1 continued to weaken the observed association between HOMA-IR and liver enzymes/PNFI in overweight or obese children. After full adjustment, associations for elevated ALT and GGT were no longer statistically significant (PRs [95% CIs] were 1.20 [0.74, 1.96] and 1.26 [0.91, 1.73], respectively) (Table 3). In a sensitivity analysis that restricted to participants who did not

report alcohol consumption in the previous 30 days, results were similar, although magnitudes of association were slightly attenuated (eTable 3).

Discussion

Among 8- to 16-year-old children of Hispanic/Latino background, insulin resistance was associated with elevated liver enzymes and PNFI. These associations were only seen in children who were overweight or obese and only remained statistically significant for AST and PNFI after mutual adjustment for several biomarkers of glucose homeostasis, inflammation, and endothelial dysfunction. Our findings suggest that liver disease may begin to develop early in the life course among obese children, and may be related to the development of insulin resistance and diabetes risk. This suggests an important focus for prevention and awareness in young Hispanics/Latinos, a population that has a high prevalence of overweight/obesity.

ALT and AST are intracellular enzymes located in the hepatocytes, although AST is less specific to hepatocytes and is abundant in muscle tissue, red blood cells, and other tissues. When detected in circulation, they indicate enzyme leakage due to liver injury. Elevated levels of GGT are associated with biliary disease and, in one pediatric study, directly correlate with the degree of hepatic fibrosis.^{40,41} The PNFI is a noninvasive index of fibrosis that has been assessed in children.⁴ However, it should be noted that children with elevated PNFI may not actually have NAFLD, and that associations of obesity-related insulin resistance with NAFLD could potentially be attributed to associations with central adiposity, which is part of the definition of PNFI. ALT levels have been shown to be highest in Hispanic/Latino adolescents compared to those of other races/ethnicities,^{24,25} and higher in males than females,²⁴ suggesting more liver damage among Hispanics/Latinos and among males. We observed here that boys were more likely to have elevated liver enzymes than girls.

The mechanism by which insulin resistance may be associated with elevated liver enzymes has not been fully delineated. The liver plays a major role in glucose metabolism. Conversely, it has been hypothesized that insulin resistance may increase both lipogenesis and the amount of free fatty acids in the liver, resulting in increased hepatic fat accumulation. This, in turn, may lead to liver injury.^{1,23,40,42} Hyperglycemia, inflammation, and decreased endothelial function may contribute to hepatocyte injury independently. Alternatively, hyperglycemia may induce inflammation and endothelial dysfunction,⁴³ which may in turn lead to decreased liver function.^{23,44} We demonstrated that sequential adjustment for biomarkers of inflammation and endothelial dysfunction attenuated the association of HOMA-IR with elevated liver enzymes, which suggests that they may be in the pathway between insulin resistance and liver injury. Furthermore, the relationship between insulin resistance and elevated liver enzymes may not be linear, and may propagate a cycle of worsening liver disease and insulin resistance.²⁰

We did not observe an association of glycemia with liver enzyme elevation in our analysis. Our study population consisted of children and adolescents, and the levels of glycemia may not have been great enough to see an association even if it were to exist. Furthermore,

HOMA-IR is a better early detector of glucose homeostasis abnormalities than either fasting glucose or HbA1c, since it precedes hyperglycemia,^{45,46} which may explain the consistency of associations we saw for HOMA-IR with liver enzymes and PNFI. Indeed, insulin resistance tends to be exacerbated during adolescence. During puberty, levels of growth hormone, IGF-1, and other related hormones are high, and a limitation of this study is the lack of measurements that may have captured the influence of these variables on the relationship between insulin resistance and NAFLD. Further studies may be able to help identify the specific period of adolescence that may be associated with the greatest risk for developing NAFLD and its metabolic sequelae.

There were several strengths and limitations of this analysis to consider. This was a cross-sectional study, so we were unable to address temporality of these relationships and could not distinguish between mediators and confounders. We were unable to include 2-hour glucose results as one of the measures of glycemia. Nor were we able to use a euglycemic hyperinsulinemic clamp technique to directly estimate insulin resistance. However, this technique is challenging to use in large epidemiologic studies and is less relevant in clinical practice. The use of HOMA-IR as a surrogate measure is justified by its linear relationship with estimates of insulin resistance as measured by the glucose clamp.⁴⁷ Lastly, liver enzymes and PNFI are not diagnostic of NAFLD. Nonetheless, they are commonly used noninvasive surrogate markers of NAFLD. An important strength of this study was that the sample was population-based and drawn from a heterogeneous mix of children and adolescents from various Hispanic/Latino backgrounds. SOL Youth is unique in that it is one of the largest studies of cardiometabolic health in Hispanic/Latino children. In the pediatric population, it is relatively uncommon for external insults such as alcohol consumption or viral liver infection to affect liver enzyme levels, and we had available an array of clinical and behavioral variables to control for confounding. Furthermore, we showed similar results among those children and adolescents who had not recently consumed alcohol.

In conclusion, we found that Hispanic/Latino children and adolescents had a high prevalence of elevated liver enzymes in general, and that the prevalence was particularly high in those who were male, overweight/obese, or exhibited central adiposity. Insulin resistance was associated with surrogate markers of NAFLD in overweight or obese Hispanic/Latino children and adolescents, and this association was partially mediated by inflammation and endothelial dysfunction. Furthermore, associations were consistent across Hispanic/Latino background. This suggests a potential target for prevention of liver disease in Hispanic/Latino youth, which is particularly important given the high prevalence of liver damage in Hispanic/Latino adults. Identifying overweight or obese Hispanic/Latino children and adolescents with insulin resistance could help detect those who are at highest risk for developing NAFLD. Further longitudinal study of these associations could better elucidate the temporal relationship between obesity, insulin resistance, and liver enzyme elevation, including the complex interplay of inflammation on glucose homeostasis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
GGT	gamma-glutamyl transpeptidase
HbA1c	hemoglobin A1c
HCHS/SOL	Hispanic Community Health Study/Study of Latinos
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPLC	high performance liquid chromatography
hs-CRP	high-sensitivity C-reactive protein
IGF-1	insulin-like growth factor-1
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
PAI-1	plasminogen activator inhibitor-1
PNFI	pediatric NAFLD fibrosis index
PR	prevalence ratio
SOL Youth	Study of Latino Youth

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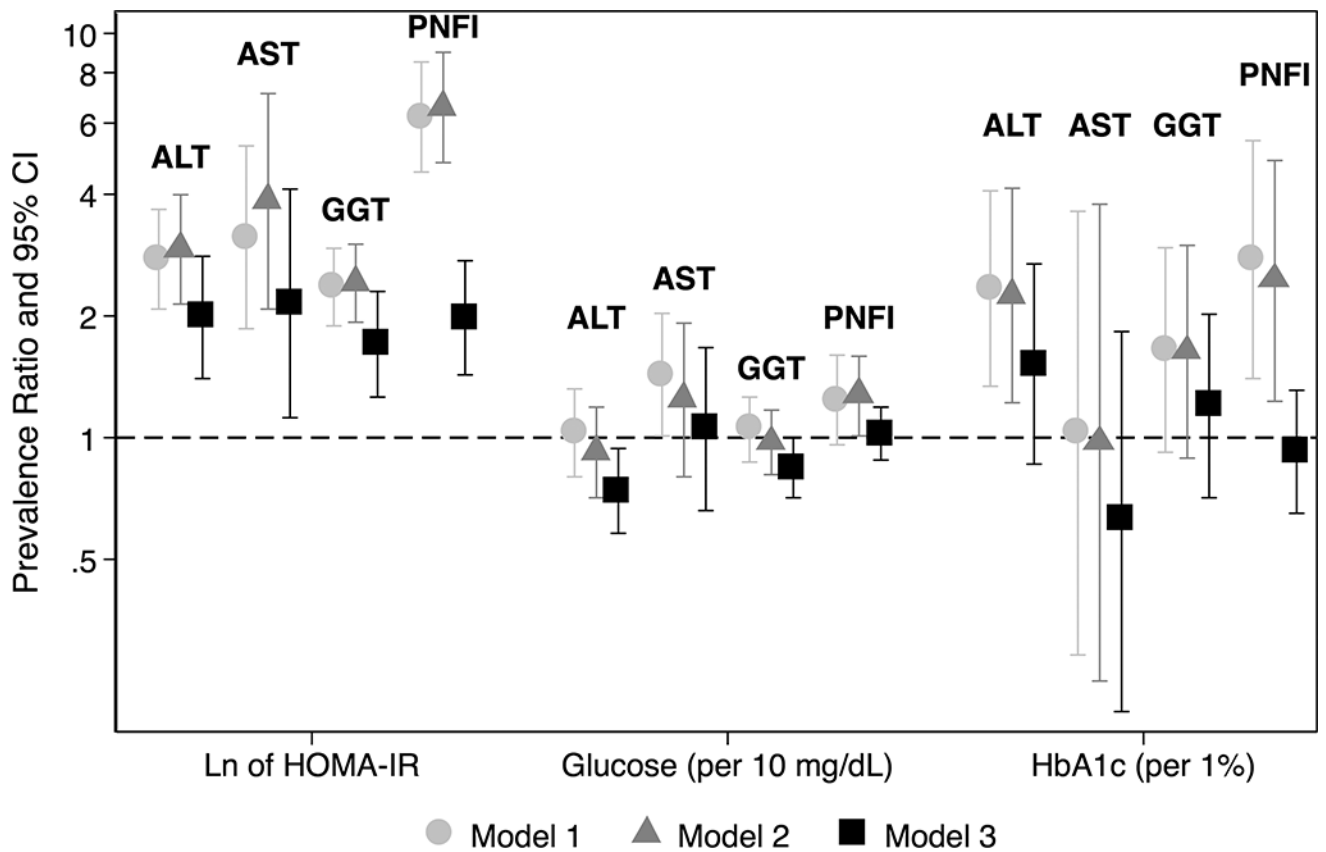


Figure. Associations of insulin resistance and hyperglycemia with elevated liver enzymes and PNFI

Elevated liver enzymes were defined as ALT >25 U/L for boys and >22 U/L for girls, AST >37 U/L, GGT >17 U/L. Elevated PNFI was defined as >9. Prevalence ratios were obtained using Poisson regression models with robust variance. We specified the models as follows: Model 1: Unadjusted; Model 2 (Sociodemographics): Model 1 + age, sex, Mexican background, field center, household income, and parental education; Model 3 (traditional risk factors): Model 2 + moderate/vigorous activity, elevated waist circumference, BMI percentile, systolic blood pressure percentile, LDL-c, HDL-c, ln of triglycerides, and pubertal status. Models for PNFI were not adjusted for age, waist circumference, or triglycerides, since PNFI is calculated using these variables.

Table 1
Study population characteristics by levels of liver enzymes and Pediatric NAFLD Fibrosis Index

	ALT*		AST		GGT		PNFI	
	25 U/L (N=1,146)	>25 U/L (N=171)	<37 U/L (N=1,266)	37 U/L (N=51)	<17 U/L (N=1,042)	17 U/L (N=275)	<9 (N=1,149)	9 (N=168)
	Weighted Mean (SE) or %	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)
Age, years	12.2 (0.1)	11.9 (0.3)	12.2 (0.1)	11.5 (0.4)	12.0 (0.1)	13.0 (0.2)	12.2 (0.1)	12.2 (0.2)
Male	50.0%	62.0%	50.7%	72.7%	48.1%	64.6%	51.1%	54.7%
Household income								
\$20, 000	53.7%	46.4%	53.1%	41.9%	52.0%	55.4%	51.6%	61.9%
\$21,000–\$40,000	31.3%	36.3%	31.4%	46.7%	32.8%	28.7%	33.5%	19.7%
>\$40,000	15.0%	17.3%	15.5%	11.5%	15.2%	15.9%	14.9%	18.3%
Parental education								
<High school	37.3%	42.1%	37.6%	46.5%	36.9%	41.7%	37.5%	41.3%
High school	29.8%	28.9%	29.7%	27.2%	30.0%	28.2%	29.3%	32.4%
>High school	32.9%	29.0%	32.7%	26.3%	33.0%	30.2%	33.2%	26.2%
Alcohol use in the past 30 days	5.3%	3.9%	5.1%	5.2%	4.6%	7.0%	4.7%	8.7%
Waist circumference 90 th percentile	9.8%	31.0%	11.7%	35.2%	8.0%	30.0%	3.5%	82.8%
BMI category								
Under/Normal weight	58.0%	26.9%	55.0%	26.8%	60.3%	30.0%	60.9%	0.4%
Overweight	20.4%	14.8%	20.1%	6.4%	20.2%	17.7%	22.0%	1.8%
Obese	21.6%	58.3%	24.8%	66.8%	19.6%	52.3%	17.1%	97.8%
Moderate/vigorous activity, minutes per day	36.2 (1.1)	31.1 (2.2)	35.6 (1.0)	33.6 (3.8)	36.5 (1.1)	31.9 (1.8)	36.7 (1.0)	27.0 (2.3)
Pubertal	59.7%	45.0%	58.3%	45.1%	56.2%	64.3%	58.0%	56.9%
Systolic BP 90 th percentile	4.1%	4.1%	4.0%	8.6%	3.8%	5.3%	4.2%	3.4%
Diastolic BP 90 th percentile	2.5%	2.0%	2.3%	5.9%	2.1%	3.7%	2.4%	2.8%
Total cholesterol, mg/dL	153 (1.1)	159 (2.7)	154 (1.1)	155 (4.3)	153 (1.2)	158 (2.5)	153 (1.1)	166 (3.0)
LDL-c, mg/dL	86 (1.0)	90 (2.3)	87 (0.9)	88 (3.8)	86 (1.0)	91 (2.0)	85 (0.9)	97 (2.6)
HDL-c, mg/dL	53 (0.5)	49 (1.1)	52 (0.4)	47 (1.9)	53 (0.5)	48 (0.8)	53 (0.5)	42 (0.8)

	ALT*		AST		GGT		PNFI	
	25 U/L (N=1,146)	>25 U/L (N=171)	<37 U/L (N=1,266)	37 U/L (N=51)	<17 U/L (N=1,042)	17 U/L (N=275)	<9 (N=1,149)	9 (N=168)
	Weighted Mean (SE) or %	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)	Weighted Mean or % (SE)
Triglycerides, mg/dL †	66 (49-91)	89 (59-126)	67 (50-93)	100 (74-116)	65 (48-89)	83 (57-129)	64 (47-86)	124 (90-171)
hs-CRP, mg/L †	0.4 (0.2-1.0)	0.9 (0.3-2.5)	0.4 (0.2-1.1)	1.4 (0.6-2.9)	0.4 (0.2-0.9)	1.1 (0.4-2.5)	0.4 (0.2-0.9)	2.1 (1.0-4.1)
Adiponectin, ng/mL	8060 (162)	6640 (484)	7935 (160)	6283 (573)	8308 (184)	6215 (231)	8211 (163)	5281 (222)
PAI-1, ng/mL †	1.8 (1.1-3.1)	3.7 (1.9-5.7)	1.9 (1.2-3.3)	4.2 (1.9-6.0)	1.8 (1.1-3.0)	3.1 (1.5-4.7)	1.7 (1.1-3.0)	3.9 (2.8-6.3)
e-selectin, ng/mL	47.7 (0.8)	65.2 (2.6)	49.2 (0.8)	70.0 (5.4)	48.4 (0.8)	55.8 (1.9)	48.1 (0.8)	64.2 (2.9)
Fasting glucose, mg/dL	91.7 (0.3)	91.8 (0.6)	91.6 (0.3)	93.6 (1.0)	91.7 (0.3)	91.9 (0.5)	91.6 (0.3)	92.8 (0.7)
Fasting glucose 100 mg/dL	10.5%	6.4%	9.9%	12.5%	10.0%	9.9%	9.3%	15.8%
HbA1c, %	5.2 (0.01)	5.3 (0.02)	5.2 (0.01)	5.3 (0.06)	5.2 (0.01)	5.3 (0.03)	5.2 (0.01)	5.3 (0.03)
HbA1c 5.7%	8.0%	6.8%	8.0%	4.2%	6.9%	11.5%	7.4%	11.0%
HOMA-IR 2.6	49.5%	74.0%	51.8%	75.7%	47.7%	71.8%	47.2%	95.0%
HOMA-IR †	2.6 (1.7-3.9)	4.4 (2.5-6.8)	2.7 (1.7-4.1)	4.7 (2.6-7.4)	2.5 (1.7-3.8)	4.3 (2.3-6.7)	2.5 (1.7-3.7)	6.3 (4.6-8.6)

Bolded values indicate $p < 0.05$ for comparison of characteristics in persons with normal versus elevated liver enzymes or PNFI. P-values were calculated using Wald tests.

* ALT cut-points for boys were 25 U/L versus >25 U/L. For girls, cut-points were 22 U/L versus >22 U/L.

† Weighted medians (25th-75th percentiles) are presented, since distributions of these variables were skewed.

Prevalence of elevated liver enzymes, elevated PNFI, hyperglycemia, and insulin resistance by age, sex, body mass index, and Hispanic/Latino background

Table 2

	ALT >25 U/L*	AST 37 U/L	GGT 17 U/L	PNFI 9	Fasting glucose 100 mg/dL	HbA1c 5.7%	HOMA-IR 2.6
	Weighted % (SE)	Weighted % (SE)	Weighted % (SE)	Weighted % (SE)	Weighted % (SE)	Weighted % (SE)	Weighted % (SE)
<i>Overall (N=1,317)</i>	12.8%	3.4%	20.5%	11.4%	10.0%	7.8%	52.6%
<i>By age</i>							
8–12 years (n=739)	14.4%	4.5%	16.1%	11.9%	10.9%	9.8%	50.7%
13–14 years (n=339)	12.3%	2.5%	22.0%	12.7%	6.9%	6.4%	60.2%
15–16 years (n=239)	9.8%	1.9%	28.9%	8.9%	11.0%	5.1%	49.9%
<i>By sex</i>							
Female (n=659)	10.0%	1.9%	15.0%	10.6%	5.7%	7.0%	58.9%
Male (n=658)	15.4%	4.8%	25.8%	12.1%	14.1%	8.6%	46.7%
<i>By BMI</i>							
Normal weight (n=674)	6.4%	1.7% (0.5)	11.4%	0.1%	8.7%	6.3%	33.5%
Overweight (n=275)	9.6%	1.1% (0.5)	18.5%	1.0%	9.1%	5.5%	56.8%
Obese (n=368)	28.3%	8.7% (2.2)	40.9%	42.3%	13.3%	12.8%	88.8%
<i>By Hispanic/Latino Background</i>							
Dominican (n=150)	5.8%	1.8%	16.0%	13.0%	4.1%	8.8%	49.5%
Puerto Rican (n=119)	9.1%	0%	25.0%	13.7%	7.4%	6.2%	51.6%
Cuban (n=94)	1.1%	0%	19.0%	3.5%	16.0%	7.9%	65.7%
Central American (n=100)	15.8%	5.0%	33.1%	8.2%	13.9%	5.8%	58.8%
Mexican (n=585)	17.2%	3.7%	19.7%	11.8%	10.5%	6.4%	53.9%
South American (n=61)	13.0%	11.4%	18.0%	10.6%	7.9%	9.0%	50.5%
Mixed/Other (n=208)	10.3%	4.5%	20.5%	11.3%	12.2%	12.9%	46.0%
<i>By Mexican Background</i>							
Non-Mexican (n=732)	8.9%	3.2%	21.3%	11.0%	9.6%	9.1%	51.6%
Mexican (n=585)	17.2%	3.7%	19.7%	11.8%	10.5%	6.4%	53.9%

*Elevated ALT was defined as >25 U/L for boys and >22 U/L for girls.

Bolded values indicate $p < 0.05$ for comparison of characteristics in persons with normal versus elevated liver enzymes, PNFI, hyperglycemia, or insulin resistance. P-values were calculated using Wald tests.

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Table 3

Associations of insulin resistance with elevated liver enzymes and PNFI, adjusted for inflammation and endothelial dysfunction biomarkers and stratified by BMI

	High ALT	High AST	High GGT	High PNFI*
	Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI)	Prevalence Ratio (95% CI)
Ln of HOMA-IR				
Under/normal weight (N=674)				
Base model [†]	1.57 (0.87, 2.84)	0.82 (0.28, 2.41)	1.53 (0.92, 2.56)	--
Additionally adjusted for adiponectin	1.58 (0.88, 2.84)	0.84 (0.28, 2.53)	1.51 (0.91, 2.52)	--
Additionally adjusted for ln hs-CRP	1.60 (0.88, 2.91)	0.86 (0.27, 2.75)	1.55 (0.91, 2.63)	--
Additionally adjusted for e-selectin	1.43 (0.76, 2.68)	0.84 (0.26, 2.70)	1.52 (0.89, 2.61)	--
Additionally adjusted for ln PAI-1	1.51 (0.79, 2.88)	0.85 (0.24, 2.95)	1.55 (0.91, 2.64)	--
Overweight or obese (N=643)				
Base model [†]	2.40 (1.61, 3.58)	4.50 (2.14, 9.48)	1.75 (1.34, 2.29)	3.12 (2.39, 4.05)
Additionally adjusted for adiponectin	2.06 (1.33, 3.17)	3.92 (1.78, 8.62)	1.59 (1.19, 2.12)	3.01 (2.31, 3.92)
Additionally adjusted for ln hs-CRP	1.88 (1.24, 2.84)	3.08 (1.51, 6.29)	1.50 (1.12, 2.00)	2.83 (2.18, 3.68)
Additionally adjusted for e-selectin	1.53 (1.01, 2.33)	2.13 (1.11, 4.08)	1.42 (1.05, 1.91)	2.77 (2.13, 3.61)
Additionally adjusted for ln PAI-1	1.20 (0.74, 1.96)	2.02 (1.09, 3.77)	1.26 (0.91, 1.73)	2.62 (1.93, 3.56)

* The model for PNFI does not include adjustment for age, waist circumference, or triglyceride levels.

[†]The base model includes adjustment for age, sex, household income, parental education, Mexican background, field center, physical activity, SBP percentile, LDL-c, HDL-c, ln of triglycerides, and pubertal status