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Predictors of liver fat among children and adolescents from five different ethnic groups

Gertraud Maskarinec[1] | Andrea K. Garber[2] | Michael C. Wong[1] | Nisa Kelly[1] | Leila Kazemi[1] | Steven D. Buchthal[1] | Nicole Fearnbach[3] | Steven B. Heymsfield[3] | John A. Shepherd[1]

[1]University of Hawaii Cancer Center, Honolulu, Hawaii, USA

[2]University of California at San Francisco, San Francisco, California, USA

[3]Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA

Correspondence
Gertraud Maskarinec, University of Hawaii Cancer Center, 701 Ilalo St, Honolulu, HI 96813, USA.
Email: gertraud@cc.hawaii.edu

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Abstract

Objectives: As rates of obesity around the world have increased, so has the detection of high level of liver fat in children and adolescents. This may put them at risk for cardiovascular disease later in life. This analysis of a cross-sectional population-based study of children and adolescents evaluated demographic and lifestyle determinants of percent liver fat.

Methods: Healthy participants (123 girls and 99 boys aged 5–17 years) recruited by convenience sampling in three locations completed questionnaires, anthropometric measurements, and dual X-ray absorptiometry and magnetic resonance imaging (MRI) assessment. General linear models were applied to estimate the association of demographic, anthropometric, and dietary factors as well as physical activity with MRI-based percent liver fat.

Results: The strongest predictor of liver fat was body mass index (BMI; $p < 0.0001$); overweight and obesity were associated with 0.5% and 1% higher liver fat levels. The respective adjusted mean percent values were 2.9 (95% CI 2.7, 3.1) and 3.4 (95% CI 3.2, 3.6) as compared to normal weight (2.4; 95% CI 2.3, 2.6). Mean percent liver fat was highest in Whites and African Americans, intermediate in Hispanic, and lowest among Asians and Native Hawaiians/Pacific Islanders ($p < 0.0001$). Age ($p = 0.67$), sex ($p = 0.28$), physical activity ($p = 0.74$), and diet quality ($p = 0.70$) were not significantly related with liver fat.

Conclusions: This study in multiethnic children and adolescents confirms the strong relationship of BMI with percent liver fat even in a population with low liver fat levels without detecting an association with age, sex, and dietary or physical activity patterns.

KEYWORDS
children, diet, ethnicity, liver fat, MRI, obesity

1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has been increasing in adults and children during recent years and may lead to an elevated risk for chronic disease development over time.[1] Among US adolescents, the suspected prevalence increased from 3.9% in 1988–1994 to 10.7% in 2007–2010.[2] Other estimates range between 5% and 10% in general population studies and 28%–41% in clinical investigations of participants with obesity.[3] The wide variations in estimates are partially due to the methods applied for diagnosis. In addition to the clinical gold standard of liver biopsy, serum biomarkers (alanine or aspartate aminotransferase [ALT/AST]) and imaging technologies are commonly used in research studies,[4,5] but larger nonclinical studies in children primarily applied ALT.[2,6]

Body mass index (BMI) is the most common significant predictor of percent liver fat.[2,3] In a British cohort of young adults, participants with overweight or obesity were 5 and 27 times more likely than those with normal weight to be diagnosed with NAFLD.[7] Determinants of liver fat beyond the strong association with BMI have been examined.[4,6] Among adults, ethnic differences have been documented with higher values among individuals with Japanese ancestry and lower values in African Americans than Whites.[8,9] In contrast, the highest levels in children and adolescents have been reported among those with Hispanic ancestry,[2,6] followed by Whites and then African Americans with a higher prevalence in girls than boys.[2,10]

Dietary intake patterns have been considered as additional determinants of NAFLD.[5,11] In adults, a higher dietary quality consisting of fruits, vegetables, whole grains and less meat, refined grains, and sugars was inversely related to liver fat after controlling for overall adiposity in several studies.[12-14] Findings in children included a positive association with a Western dietary pattern consisting of higher amounts of fast food and sweets and low content of whole grains, fruits, and vegetables in Australian adolescents,[11] an inverse relationship with the intake of cereals and a positive association of NAFLD prevalence with sugar-sweetened beverages in Spanish children,[15] and a positive relationship with total energy intake.[16] In a randomized trial with a low sugar diet compared to a standard diet, hepatic steatosis in adolescent boys decreased significantly during an 8-week period.[10] The evidence for a separate influence of physical activity on liver fat beyond its beneficial effect on BMI status is uncertain. A meta-analysis of combined diet-physical activity interventions suggests improvement in BMI level, liver enzymes, and NAFLD in children,[17] but it is not clear what type and level of physical activity should be recommended in children.[18]

To add to the limited evidence based on imaging, the association between liver fat obtained by magnetic resonance imaging (MRI) was examined in a community-based sample of children and adolescents[19] with a substantial sample size as compared to published MRI studies among minors without a diagnosis of NAFLD or other conditions.[20,21] The objective was to describe differences in liver fat across ethnic groups in girls and boys, to determine the relationship of other adiposity measures with percent liver fat, and to evaluate the association of diet quality with liver fat. The underlying hypothesis was that higher percent liver fat is associated with male sex, Asian ethnicity, overweight/obesity, and lower diet quality and physical activity levels.

2 | METHODS

2.1 | Study population

The Shape Up! Kids Study aims to provide pediatric phenotype descriptors of health using tools to quantify body shape, which allow personal health assessment. This ongoing investigation has the goal to recruit 720 children, ages 5 to 17 years.[19] The current analysis is based on a partial sample. To obtain a diverse study sample, enrollment was stratified by age (5–9 years, 10–14 years, and 15–17 years), ethnicity (non-Hispanic White, non-Hispanic African American, Hispanic, Asian, and Native Hawaiian or Other Pacific Islander [NHOPI]), sex, BMI-Z score (<-1, -1 to 1, 1 to 1.6, and >1.6), and location (San Francisco, CA, Baton Rouge, LA, or Honolulu, HI). Participants were recruited by convenience sampling via flyers, news broadcasts, health fairs, and word of mouth, had to be ambulatory, and meet the study strata requirements. Exclusion criteria included pregnancy, missing limbs, presence of significant nonremovable metal in the body, or a history of body-altering surgery. Participants were compensated for their time with $50–$100, depending on the site. Human subjects approval was obtained from the Institutional Review Boards at the three locations Pennington Biomedical Research Center (PBRC, IRB study #2017-10, FWA #00006218), University of California, San Francisco (UCSF, IRB #16-20197), and University of Hawaii Office of Research Compliance (UH ORC, CHS #24282). Both parents, with the exception of single parents or parents who were physically unable attend due to medical reasons, gave informed consent. Children 7–17 years old provided written assent and those 5–6 years old gave verbal assent.

2.2 | Study design

Participants were instructed to fast without food for at least 8 h (water and prescription medications were allowed) before the visit at the UCSF Clinical and Translational Science Institute, PBRC, or the University of Hawaii Cancer Center (UHCC) Body Composition Laboratory.

Questionnaires included an online version of the Health Behavior in School-Aged Children (HBSC) survey[22] and the Physical Activity Questionnaire for Older Children or Adolescents.[23] Manual anthropometric measures according to the standard protocol from National Health and Nutrition Examination Survey (NHANES), 3D Optical Imaging, whole-body DXA, fasting blood draw, strength assessments, and whole-body MRI were completed at an in-person visit.[19] Pubertal development was assessed using self-reported Tanner stages.[24]

2.3 | Anthropometrics

Among other measures, body weight, height, and waist circumference were assessed at the study visit. Percentile scores according to Centers for Disease Control and Prevention (CDC) growth charts[25] and sex-specific BMI-for-age values were computed. To create BMI categories, the following cutoffs were used: Normal weight <85 percentile, overweight ≥85 percentile, and obesity ≥95 percentile of BMI-for-age and sex.[26]

2.4 | MRI acquisition

MRI scans were performed within the MRI Systems at PBRC, UCSF, and UHCC using a protocol designed to segment the major tissue compartment volumes for the whole body, including adipose, muscle, and bone. One volunteer was scanned at UHCC and PBRC with comparable results. Measures were regionally subdivided by limbs and trunk, visceral, and liver volumes and further subdivisions were related to the components of these volume regions (fat and water). All participants wore light clothing without metal objects while undergoing the whole-body MRI protocol and were instructed to complete holding their breath during the abdominal sections to minimize motion artifacts in the image. This MRI protocol has a short scan time due to children being less tolerant of the discomforts associated with an MR scan (feelings of claustrophobia and by loud noises from the scanner) because supine positioning was used. The scans were acquired using 2.6-mm contiguous axial slices (adequate for VAT, NAFLD, and whole organs) for T1-weighted and chemical shift based water-fat separation acquisitions at the same resolution with the multi-peak fat spectrum model and single T2* correction. The fat-water separated protocols have different names: IDEAL for the GE 3T system at PBRC and UCSF, and TI VIBE for the Siemen's 3T at UHCC.

2.5 | Assessment of liver fat

Analysis of the images was centrally performed at UHCC by a trained technologist. For liver fat, region of interest (ROI) selection within the liver followed the methods of Fishbein[27] using Fiji to select two regions of liver tissue (8–15 mm^3) from the water image, while avoiding major blood vessels and breathing artifacts.[28] Intensities were collected from the identical regions of the fat image. Fat percentages were calculated as $S_f/(S_f + S_w)$.

2.6 | Dual energy X-ray absorptiometry

Participants completed one whole-body dual energy X-ray absorptiometry (DXA) scan on a Hologic Discovery/A or Horizon/A system (Hologic Inc.). As described in detail previously,[19] DXA scans were all centrally analyzed at UHCC by a trained technologist using Hologic APEX version 5.6 with the (NHANES) Body Composition Analysis calibration option disabled. DXA cross-calibration phantoms were circulated between all sites and calibration equations derived to remove systematic bias in all bone and soft tissue results. Among other measures, total and percent body fat were derived.

2.7 | Diet and physical activity assessment

Food consumption frequencies for four items were collected by self-report or by the parents using the HBSC questionnaire[22,29]: fruits, vegetables, sweets (candy or chocolate), and soft drinks that contain sugar. The question was, “How many times a week do you usually eat or drink.?” with 7 possible categories from “never” to “every day more than once”. To create an indicator variable for diet quality, all frequencies were assigned a score from 0 to 14 to take into account the nonlinear increase in intake frequency across categories as opposed to the simple scoring approach used by some HBSC investigations.[30] The scores for fruit and vegetables (FV) and those for sweets and sugar-sweetened drinks (SS) were added to assess a desirable food category and an unfavorable category. To obtain approximately equal-sized categories, the summary scores were divided into a low and high category (10 and 4/week as respective cutoffs) and combined into an overall score with four levels as follows: High SS/Low FV, Low SS/Low FV, High SS/High FV, and Low SS/High FV. An overall measure of general physical activity was obtained as the mean of nine individual scores for the self-reported frequency of different activities.[23]

2.8 | Statistical Analysis

Of 302 participants recruited so far, 48 had missing values for liver fat because participants declined the MRI or the image could not be analyzed due to artifacts from breathing or movement, 37 had invalid information on one of the four dietary variables, and 5 were missing DXA measures (some overlap of missing occurred). Therefore, the final analysis set included 222 girls and boys. As the number of participants with NAFLD was too low for analysis, a high liver fat variable was created using the median of 2.68% as cut point to maximize the number of participants per group to obtain stable models. In this population of generally healthy youth from the community, only a small proportion were classified as NAFLD, but population-based studies have shown that accumulation of liver fat at young age is of interest even if the definition of NAFLD is not met.[31,32] Therefore, the terms terminology low versus high liver fat were chosen. The physical activity score was categorized into low and high (cut point = 2.5) while the 60 participants with incomplete information were coded as missing. Descriptive statistics of the study population, mean adiposity measures by sex and ethnicity, and Spearman correlation coefficients of liver fat with height, BMI, waist circumference, DXA total and percent body fat were computed.

TABLE 1 Characteristics of children and adolescents in the Shape Up! Kids Study[a]

Characteristic	Category	Girls	Boys	All
N (%)		123 (55)	99 (45)	222 (100)
Age, years		12.3 ± 3.4	12.1 ± 3.1	12.2 ± 3.2
Ethnicity (%)	White	34 (28)	38 (39)	72 (32)
	African American	37 (30)	25 (25)	62 (28)
	Hispanic	14 (11)	8 (8)	22 (10)
	Asian	14 (11)	10 (10)	24 (11)
	NHOPI	24 (20)	18 (18)	42 (19)
Tanner stage (%)[b]	1	32 (28)	33 (35)	65 (31)
	2	13 (12)	14 (15)	27 (13)
	3	20 (18)	13 (14)	33 (16)
	4	22 (20)	23 (24)	45 (22)
	5	25 (22)	11 (12)	36 (18)
BMI (%)	Normal weight	62 (50)	64 (65)	126 (57)
	Overweight	27 (22)	17 (17)	44 (20)
	Obesity	34 (28)	18 (18)	52 (23)
Weight, kg		51.9 ± 20.7	50.5 ± 19.9	51.3 ± 20.3
Height, cm		149.3 ± 15.7	152.7 ± 19.0	150.8 ± 17.3
Waist circumference, cm		77.7 ± 16.7	73.3 ± 14.0	75.7 ± 15.5
BMI-for-age percentile, %		72 ± 29	64 ± 29	69 ± 29
DXA total body fat, kg		17.1 ± 10.3	11.8 ± 7.6	14.7 ± 9.6
DXA % total body fat, %		31.1 ± 7.4	22.8 ± 9.0	27.4 ± 9.1
DXA visceral fat area, kg		38.0 ± 27.7	42.3 ± 17.0	39.9 ± 23.6
MRI liver fat, %		2.8 ± 0.9	2.8 ± 0.9	2.8 ± 0.9
Physical activity score[b]		2.6 ± 0.7	3.0 ± 0.7	2.8 ± 0.7
FV (%)	<10/week	73 (59)	56 (57)	129 (58)
	10+/week	50 (41)	43 (43)	93 (42)
Sweets & SS (%)	<4/week	56 (46)	50 (51)	106 (48)
	4+/week	67 (54)	49 (49)	116 (52)
Diet quality (%)	High SS, low FV	47 (38)	26 (26)	73 (33)
	Low SS, low FV	26 (21)	30 (31)	56 (25)
	High SS, high FV	20 (16)	23 (23)	43 (19)
	Low SS, high FV	30 (25)	20 (20)	50 (23)

Abbreviations: BMI, body mass index; DXA, dual X-ray absorptiometry; FV, fruit and vegetables; MRI, magnetic resonance imaging; NHOPI, Native Hawaiian/Other Pacific Islander; SS, sugar-sweetened drinks.

[a]Means ± standard deviations are shown unless otherwise indicated.

[b]Missing values for Tanner stage ($N = 16$) and physical activity score ($N = 60$).

General linear regression was applied to evaluate the relation of age, sex, ethnicity (Whites as reference), diet quality (High SS/Low FV as reference), physical activity, and BMI-for-age (normal weight as reference) or DXA percent total body fat, with percent liver fat with all variables in the same model. To explore potential independent associations of FV or SS intake, separate models with one of the two variables as exposure were examined. To assess possible interactions between weight status and ethnicity, a combined variable using the five ethnic groups and normal weight versus overweight/obesity was created.[33] The numbers of participants by ethnic group were too small to separate overweight and obesity. Using this variable, the adjusted means of liver fat were computed and plotted. Finally,

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TABLE 2 Body fat measures by ethnic group in girls and boys of the Shape Up! Kids Study[a]

Characteristic	Ethnicity	Girls	Boys	*p*-value[b]
MRI percent liver fat, %	White	3.0 ± 0.9	3.1 ± 0.9	-
	African American	3.2 ± 0.8	2.9 ± 0.8	-
	Hispanic	2.7 ± 0.6	2.9 ± 1.3	-
	Asian	2.2 ± 0.6	2.4 ± 0.5	-
	NHOPI	2.3 ± 0.9	2.2 ± 0.6	<0.0001
Weight, kg	White	49.7 ± 20.2	51.9 ± 18.1	-
	African American	58.7 ± 24.0	51.1 ± 19.1	-
	Hispanic	51.4 ± 17.7	41.7 ± 22.9	-
	Asian	42.3 ± 12.3	51.3 ± 16.6	-
	NHOPI	50.4 ± 19.5	50.2 ± 25.4	0.27
Height, cm	White	149.4 ± 19.0	153.9 ± 18.5	-
	African American	150.5 ± 12.9	152.5 ± 16.5	-
	Hispanic	150.5 ± 14.8	143.6 ± 24.9	-
	Asian	147.1 ± 15.6	157.4 ± 16.0	-
	NHOPI	147.7 ± 16.1	151.9 ± 22.4	0.92
BMI-for-age percentile, %	White	69 ± 32	61 ± 33	-
	African American	83 ± 21	72 ± 23	-
	Hispanic	63 ± 37	52 ± 33	-
	Asian	55 ± 29	63 ± 25	-
	NHOPI	74 ± 28	65 ± 25	0.01
Waist circumference, cm	White	76.1 ± 14.9	74.6 ± 14.6	-
	African American	81.2 ± 19.9	73.3 ± 14.0	-
	Hispanic	78.0 ± 16.0	68.3 ± 13.4	-
	Asian	71.0 ± 10.1	70.3 ± 9.3	-
	NHOPI	78.1 ± 15.6	74.1 ± 15.5	0.39
DXA total body fat, kg	White	16.1 ± 9.1	12.7 ± 8.1	-
	African American	20.6 ± 13.1	12.8 ± 7.6	-
	Hispanic	17.9 ± 9.4	8.6 ± 6.4	-
	Asian	11.7 ± 4.6	9.8 ± 4.8	-
	NHOPI	15.7 ± 8.7	11.0 ± 8.3	0.04
DXA % total body fat, %	White	31.1 ± 6.4	23.9 ± 10.4	-
	African American	32.5 ± 9.0	24.6 ± 9.6	-
	Hispanic	32.8 ± 7.6	20.0 ± 6.0	-
	Asian	27.3 ± 5.3	19.1 ± 5.2	-
	NHOPI	30.0 ± 6.6	21.4 ± 7.3	0.07
DXA visceral fat area, kg	White	40.3 ± 29.9	43.9 ± 19.1	-
	African American	42.2 ± 30.1	43.9 ± 18.1	-
	Hispanic	40.6 ± 30.4	41.5 ± 21.7	-
	Asian	27.9 ± 13.7	35.7 ± 7.7	-
	NHOPI	32.7 ± 24.9	40.5 ± 12.0	0.20

Abbreviations: BMI, body mass index; DXA, dual X-ray absorptiometry; MRI, magnetic resonance imaging; NHOPI, Native Hawaiian/Other Pacific Islander.

[a]Means ± standard deviations are shown unless otherwise indicated.

[b]*p*-value for difference across ethnic categories adjusted for sex derived by general linear models.

logistic regression was applied to estimate prevalence odds ratios (POR) and 95% confidence limits associated with high liver fat (≥2.68%) not NAFLD (≥5%) for the combined variable with the White normal weight group as reference.

3 | RESULTS

The study (Table 1) included 123 girls and 99 boys with a mean age of 12.2 ± 3.3 (range: 5–17) years. Of these, 140 were enrolled at PBRC, 79 at UHCC, and 3 at UCSF. The ethnic distribution was 32% White, 28% African American, 10% Hispanic, 11% Asian, and 19% NHOPI. Approximately 57% of participants were normal weight, 20% were overweight, 23% had obesity based on the CDC's sex-specific BMI-for-age percentile classification with a higher proportion of obesity among girls than boys. Mean liver fat values were similar in girls (2.8 ± 0.9%) and boys (2.8 ± 0.9%), while girls had higher total and percent body fat, and waist circumference. Only 3% of the study population ($N = 6$) were classified as NAFLD (≥5% liver fat): 10% of persons with obesity ($N = 5$) and 2% of those with overweight (N = 1).

Percent liver fat differed significantly by ethnicity ($p < 0.0001$) with a 27% difference between African Americans and NHOPIs. Whites (3.0 ± 0.9 and 3.1 ± 0.9%) and African Americans (3.2 ± 0.8 and 2.9 ± 0.7%) had the highest percent liver fat in girls and boys (Table 2) and Hispanics (2.7 ± 0.6 and 2.9 ± 1.3%) were intermediate, whereas Asians (2.2 ± 0.6 and 2.4 ± 0.5%) and NHOPIs (2.3 ± 0.9 and 2.2 ± 0.6%) had the lowest values. Of the other adiposity measures, only the BMI-for-age percentile ($p = 0.01$) and DXA total body fat ($p = 0.04$) differed significantly by ethnic group.

Percent liver fat was significantly related to BMI, body weight, waist circumference, total body fat, and visceral fat but not height (Table 3). The correlations were generally higher in girls than boys, but the association was strongest with BMI-for-age ($r_s = 0.51$ and $r_s = 0.42$ for girls and boys, respectively).

Participants of Asian and NHOPI ancestry had significantly lower values of liver fat than the other groups. The respective adjusted mean values were 2.7 and 2.4% for Asians and NHOPIs, 3.0% for Hispanics, and 3.2% for Whites and African Americans (Table 4). The strongest predictor of liver fat was BMI ($p < 0.0001$). Compared to normal weight participants (2.4%, 95% CI 2.3, 2.6), those with overweight (2.9%, 95% CI 2.7, 3.1) and obesity (3.4%, 95% CI 3.2, 3.6) had higher mean liver fat levels. An interaction term of BMI with ethnicity was not significant ($p = 0.93$). Among the possible determinants of percent liver fat in this study, age ($p = 0.67$), sex ($p = 0.28$), physical activity ($p = 0.95$), and diet quality ($p = 0.70$) did not show a significant association in fully adjusted models. After replacing BMI with DXA percent body fat, the model did not change substantially except that sex became significant ($p = 0.01$). However, r^2 was higher for the BMI than the DXA percent body fat model (0.36 vs. 0.30).

When modeling the combined ethnicity/BMI status variable (Figure 1), the strong differences in between children/adolescents with normal and overweight/obesity BMI-for-age became apparent.

TABLE 3 Relation of adiposity measures with levels of liver fat in the Shape Up! Kids Study

	Girls		Boys	
Characteristic	ρ[a]	p-value	ρ[a]	p-value
Weight, kg	0.308	0.001	0.224	0.026
Height, m	0.003	0.977	−0.037	0.714
Waist circumference, cm	0.286	0.001	0.288	0.004
BMI-for-age percentile, %	0.506	<0.0001	0.431	<0.0001
DXA total body fat, kg	0.367	<0.0001	0.348	0.0004
DXA % total body fat	0.457	<0.0001	0.358	0.0003
DXA visceral fat, kg	0.381	<0.0001	0.380	0.0001

Abbreviations: BMI, body mass index; DXA, dual X-ray absorptiometry.
[a]Spearman correlation coefficients are shown.

Among Whites, African Americans, and Hispanics, the mean difference in percent liver fat was close to 1% and the CIs did not overlap. Participants with Asian and NHOPI ancestry had lower percent liver fat and the difference by BMI status was only around 0.5% with overlapping CIs. PORs (Figure 2) indicated the likelihood of having high liver fat in comparison to White girls and confirmed the influence of BMI-for-age status across ethnic groups across.

Adding Tanner stage as indicator of sexual maturation to the model did not substantially change the results: BMI and ethnicity remained the only significant predictors of percent liver fat (data not shown).

4 | DISCUSSION

The current investigation of liver fat in children and adolescents is one of the first population-based studies to apply MRI assessment. The study is unique in its wide age range and ethnic composition. BMI status and ethnic background emerged as the two factors significantly associated with percent liver fat. The findings by ethnic group were unexpected as levels were lowest among Asians and NHOPIs and highest among African Americans and Whites with intermediate values in Hispanics. As expected, girls and boys with overweight and obesity had higher percent liver fat than normal weight participants. The strong association with BMI was detected despite the relatively low levels of liver fat (median = 2.68%) and the fact that only 3% of participants were classified as having NAFLD (>5%). No significant differences by age and sex were observed. Based on the limited nutritional and physical activity information, diet quality and activity score were not associated with the presence of liver fat.

In comparison to the literature, a lower prevalence of NAFLD (3%) among children and adolescents than the 7.6% estimate in the general population reported by a recent meta-analysis was detected.[3] While assessment approaches also contribute to differences, studies using MRI typically report *higher* prevalence than those using serum ALT.[2,3,6] Thus, the most likely explanation for the low NAFLD

TABLE 4 Determinants of liver fat in the Shape Up! Kids Study[a]

Model	Characteristic	Category	*B*	Std Error	*p*-value
1: BMI ($r^2 = 0.36$)	Age	Years	−0.008	0.019	0.67
	Sex (Ref = Girls)		0.111	0.102	0.28
	BMI (Ref = Normal weight)	Overweight	0.461	0.130	0.0005
		Obesity	0.967	0.126	<0.0001
	Ethnicity (Ref = White)	African American	0.017	0.131	0.90
		Hispanic	−0.142	0.183	0.44
		Asian	−0.460	0.178	0.01
		NHOPI	−0.766	0.143	<0.0001
	Diet quality	Low SS, low FV	0.003	0.135	0.98
	(Ref = High SS, low FV)	High SS, high FV	0.156	0.146	0.29
		Low SS, high FV	0.016	0.138	0.91
	Physical activity (Ref = Low[b])	High	−0.041	0.125	0.74
2: DXA % body fat ($r^2 = 0.30$)	Age	Years	−0.009	0.020	0.66
	Sex (Ref = Girls)		0.306	0.119	0.01
	DXA percent body fat	%	0.039	0.007	<0.0001
	Ethnicity (Ref = White)	African American	0.026	0.137	0.85
		Hispanic	−0.181	0.192	0.35
		Asian	−0.511	0.186	0.007
		NHOPI	−0.699	0.151	<0.0001
	Diet quality	Low SS, low FV	0.110	0.139	0.43
	(Ref = High SS, low FV)	High SS, high FV	0.166	0.153	0.28
		Low SS, high FV	0.053	0.145	0.72
	Physical activity (Ref = Low[b])	High	0.113	0.133	0.40

Abbreviations: BMI, body mass index; DXA, dual X-ray absorptiometry; FV, fruit and vegetables; MRI, magnetic resonance imaging; NHOPI, Native Hawaiian/Other Pacific Islander; PAQ, Physical Activity Questionnaire; SS, sugar-sweetened drinks.

[a]Obtained through general linear regression adjusted for age, sex, ethnicity, physical activity, diet quality, BMI or DXA percent body fat.

[b]Cutpoint is median of PAQ score.

rates reported here is the better health status in this population-based study as compared to the general population due to the recruitment through community-based strategies. Nevertheless, studies of children and adolescents have shown that liver fat co-occurs with cardiometabolic risk factors[31] and longitudinal studies have documented the trajectory of adult NAFLD beginning in childhood.[32] Therefore, the accumulation of liver fat at young age is of interest even if the definition of NAFLD is not met. In fact, population-based studies have shown that children with higher liver fat (but still < 5%) have a higher odds of cardiometabolic risk including higher blood pressure, fasting insulin, total cholesterol, triglycerides and C-reactive protein as compared to those with lower liver fat.[34]

Our finding of the highest liver fat in White children and lowest in Asian children contrasts with studies in both adults and children, which reported higher liver fat associated with Asian ancestry[8] and Hispanic background[2,6] than Whites. In an earlier study of children/adolescents with obesity and similar age, no liver fat was detectable in African Americans, whereas percent liver fat was twofold higher than normal in both Caucasians and Hispanics.[35] The lack of ethnic variation in total body fat and visceral fat is also surprising in light of previous reports.[36,37] Although selection bias may potentially be responsible for our results, it is also possible that the children and adolescents in the geographic locations for this study are exposed different nutritional and lifestyle than in previous investigations.

In agreement with previous evidence,[3,7] a large difference in liver fat by BMI status emerged in this population. Increasing proportions of suspected liver fat based on liver enzyme measurements with higher BMI have been described for adolescents who were part of NHANES[2] and for Korean youth.[38] A large meta-analysis[3] described the estimated risks of developing NAFLD as 13 and 18 times higher for participants with overweight and obesity. However, the liver fat estimates differ considerably by assessment method. One recent study that

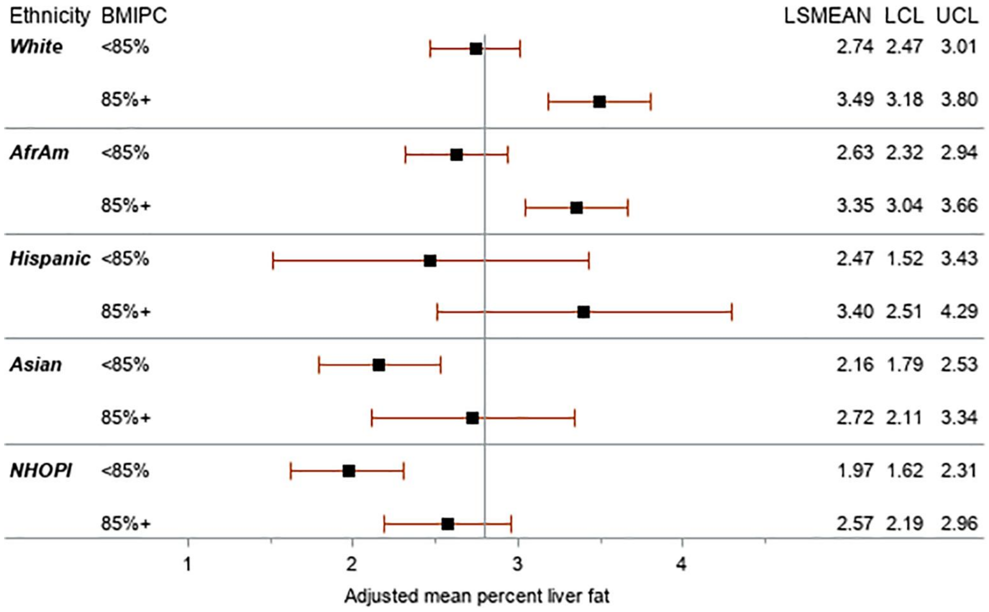

FIGURE 1 Adjusted mean percent liver fat by ethnicity and weight Status. Least square means with lower (LCL) and upper (UCL) 95% confidence limits obtained by general linear regression adjusted for age, sex, physical activity, and diet quality and stratified by body mass index percentile (BMIPC); overall mean = 2.8, NHOPI, Native Hawaiian/Other Pacific Islander

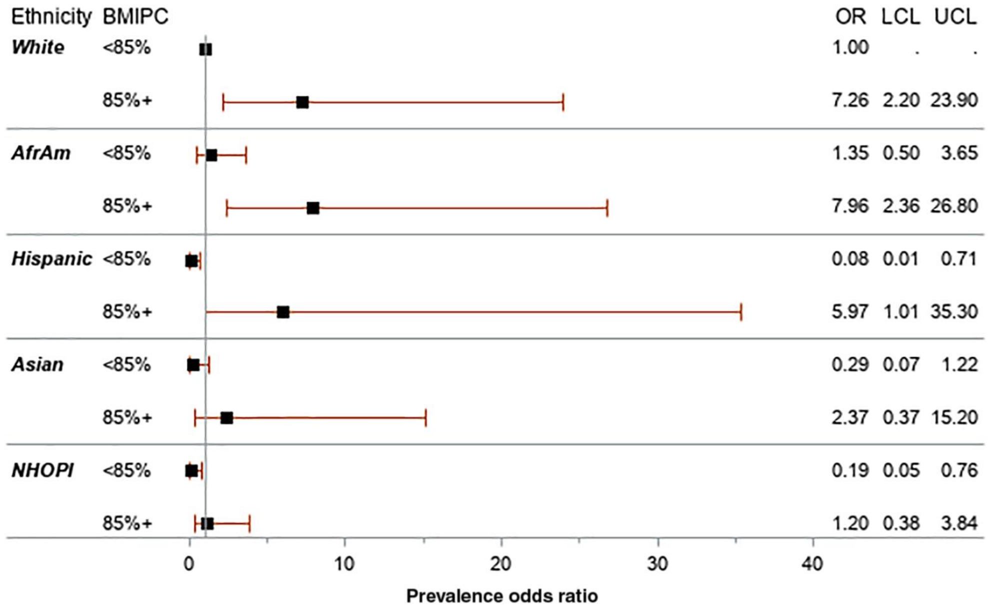

FIGURE 2 Prevalence odds ratio (POR) for high liver fat (≥2.68%) by ethnicity and weight status. POR with lower (LCL) and upper (UCL) 95% confidence limits obtained by logistic regression adjusted for age, sex, physical activity, and diet quality with white normal weight participants as reference and stratified by body mass index percentile (BMIPC). NHOPI, Native Hawaiian/Other Pacific Islander

applied MRI to 25 participants aged 9–16 years reported a 2.4-fold higher liver fat fractions when comparing participants with obesity to the normal weight category.[39] Prevalence estimates in children and adolescents with obesity, however, report much higher proportions of NAFLD than the 10% among participants with obesity in our study.[3] An interesting report from Mexico found that maternal weight status might be related to fatty liver content in their children as young adults after controlling for their own BMI.[40] Our findings do not agree with a report showing that waist circumference, a measure of abdominal adiposity, was a stronger predictor of liver fat than BMI among a study of adolescents.[41]

Prior investigations with more detailed dietary information than the current report have found associations between NAFLD and dietary patterns including a Western dietary pattern characterized by fast foods with high sugar and fat content,[11] sugar and sugar-sweetened beverages,[4,15,17] and total energy.[16] Similar to previous reports,[15,18] no association with physical activity was found, however the large number of missing scores limit the validity of our finding.

The current investigation has several strengths, foremost the MRI-based measurement of liver fat in a substantial sample size of generally healthy children and adolescents. Previous population surveys classified children and adolescents according to ALT concentrations,[2,6] whereas MRI-based investigations focused on children with overweight/obesity.[15,39,41,42] The wide age range, the ethnic diversity, and the substantial proportion of participants with overweight and obesity included by design make these findings applicable to a more general population. The most severe limitation is the lack of detailed diet and physical activity information for all participants due to constraints in the length and rigor of the self-report questionnaires. An objective method of physical activity assessment, for example, accelerometers, would have been desirable but not feasible due to logistical issues. The unexpected findings by ethnicity would likely need a larger sample size to be clarified.

5 | CONCLUSIONS

These results in children and adolescents with different ethnic backgrounds confirm the strong association of BMI with percent liver fat as assessed by MRI imaging, even in this healthy population recruited from the general population with very low levels of liver fat. Although the simple measure of diet quality was not directly related to liver fat, it is possible that nutritional factors affect liver indirectly through body weight.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

SBH and JAS designed the study, obtained funding, and directed the data collection. AKG and NF contributed to the research protocol. NS and LK were instrumental in data collection and management. SDB performed liver fat measurements. GM and AKG developed the ideas and outlined the plan for the current analysis. GM and MCW analyzed the data. GM wrote the first draft of the manuscript. All authors critically reviewed the paper and had final approval of the submitted and published versions.

ORCID

Gertraud Maskarinec https://orcid.org/0000-0002-8129-958X
Michael C. Wong https://orcid.org/0000-0003-2392-9253
Nicole Fearnbach https://orcid.org/0000-0001-9208-830X
Steven B. Heymsfield https://orcid.org/0000-0003-1127-9425

REFERENCES

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology*. 2016;64:73-84.
2. Welsh JA, Karpen S, Vos MB. Increasing prevalence of nonalcoholic fatty liver disease among United States adolescents, 1988-1994 to 2007-2010. *J Pediatr* 2013;162:496-500.
3. Anderson EL, Howe LD, Jones HE, Higgins JP, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: a systematic review and meta-analysis. *PLoS One*. 2015;10:e0140908.
4. Temple JL, Cordero P, Li J, Nguyen V, Oben JA. A guide to non-alcoholic fatty liver disease in childhood and adolescence. *Int J Mol Sci*. 2016;17:946.
5. Ko JS. New perspectives in pediatric nonalcoholic fatty liver disease: epidemiology, genetics, diagnosis, and natural history. *Pediatr Gastroenterol Hepatol Nutr*. 2019;22:501-510.
6. Schwimmer JB, McGreal N, Deutsch R, Finegold MJ, Lavine JE. Influence of gender, race, and ethnicity on suspected fatty liver in obese adolescents. *Pediatrics*. 2005;115:e561-e565.
7. Abeysekera KWM, Fernandes GS, Hammerton G, et al. Prevalence of steatosis and fibrosis in young adults in the UK: a population-based study. *Lancet Gastroenterol Hepatol*. 2020;5:295-305.
8. Lim U, Monroe KR, Buchthal S, et al. Propensity for intra-abdominal and hepatic adiposity varies among ethnic groups. *Gastroenterology*. 2019;156:966-975.
9. Nazare JA, Smith JD, Borel AL, et al. Ethnic influences on the relations between abdominal subcutaneous and visceral adiposity, liver fat, and cardiometabolic risk profile: the international study of prediction of intra-abdominal adiposity and its relationship with cardiometabolic risk/intra-abdominal adiposity. *Am J Clin Nutr*. 2012;96:714-726.
10. Schwimmer JB, Ugalde-Nicalo P, Welsh JA, et al. Effect of a low free sugar diet vs usual diet on nonalcoholic fatty liver disease in adolescent boys: a randomized clinical trial. *JAMA*. 2019;321:256-265.
11. Oddy WH, Herbison CE, Jacoby P, et al. The Western dietary pattern is prospectively associated with nonalcoholic fatty liver disease in adolescence. *Am J Gastroenterol*. 2013;108:778-785.
12. Maskarinec G, Lim U, Jacobs S, et al. Diet quality in midadulthood predicts visceral adiposity and liver fatness in older ages: the multiethnic cohort study. *Obesity (Silver Spring)*. 2017;25:1442-1450.
13. Chan R, Wong VW, Chu WC, et al. Diet-quality scores and prevalence of nonalcoholic fatty liver disease: a population study using proton-magnetic resonance spectroscopy. *PLoS One*. 2015;10:e0139310.
14. Chung GE, Youn J, Kim YS, et al. Dietary patterns are associated with the prevalence of nonalcoholic fatty liver disease in Korean adults. *Nutrition*. 2019;62:32-38.
15. Arenaza L, Medrano M, Oses M, et al. Dietary determinants of hepatic fat content and insulin resistance in overweight/obese children: a cross-sectional analysis of the Prevention of Diabetes in Kids (PREDIKID) study. *Br J Nutr*. 2019;121:1158-1165.
16. Anderson EL, Howe LD, Fraser A, et al. Childhood energy intake is associated with nonalcoholic fatty liver disease in adolescents. *J Nutr*. 2015;145:983-989.

17. Utz-Melere M, Targa-Ferreira C, Lessa-Horta B, Epifanio M, Mouzaki M, Mattos AA. Non-alcoholic fatty liver disease in children and adolescents: lifestyle change - a systematic Review and meta-analysis. *Ann Hepatol*. 2018;17:345-354.
18. Gibson PS, Lang S, Dhawan A, et al. Systematic review: nutrition and physical activity in the management of paediatric nonalcoholic fatty liver disease. *J Pediatr Gastroenterol Nutr*. 2017;65: 141-149.
19. Wong MC, Ng BK, Kennedy SF, et al. Children and adolescents' anthropometrics body composition from 3-D optical surface scans. *Obesity (Silver Spring)*. 2019;27:1738-1749.
20. Schwimmer JB, Middleton MS, Behling C, et al. Magnetic resonance imaging and liver histology as biomarkers of hepatic steatosis in children with nonalcoholic fatty liver disease. *Hepatology*. 2015;61: 1887-1895.
21. Middleton MS, Van Natta ML, Heba ER, et al. Diagnostic accuracy of magnetic resonance imaging hepatic proton density fat fraction in pediatric nonalcoholic fatty liver disease. *Hepatology*. 2018;67: 858-872.
22. Roberts C, Freeman J, Samdal O, et al. The Health Behaviour in School-aged Children (HBSC) study: methodological developments and current tensions. *Int J Public Health*. 2009;54(Suppl. 2): 140-150.
23. Crocker PR, Bailey DA, Faulkner RA, Kowalski KC, McGrath R. Measuring general levels of physical activity: preliminary evidence for the Physical Activity Questionnaire for Older Children. *Med Sci Sports Exerc*. 1997;29:1344-1349.
24. Duke PM, Litt IF, Gross RT. Adolescents' self-assessment of sexual maturation. *Pediatrics*. 1980;66:918-920.
25. National Center for Health Statistics. *Clinical Growth Charts*. Atlanta, GA: Centers for Disease Control and Prevention; 2017. https://www.cdc.gov/growthcharts/clinical_charts.htm.
26. Must A, Anderson SE. Body mass index in children and adolescents: considerations for population-based applications. *Int J Obes (Lond)*. 2006;30:590-594.
27. Fishbein MH, Miner M, Mogren C, Chalekson J. The spectrum of fatty liver in obese children and the relationship of serum aminotransferases to severity of steatosis. *J Pediatr Gastroenterol Nutr*. 2003;36:54-61.
28. Schindelin J, Arganda-Carreras I, Frise E, et al. Fiji: an open-source platform for biological-image analysis. *Nat Methods*. 2012;9: 676-682.
29. Roberts RA, Laskin DL, Smith CV, et al. Nitrative and oxidative stress in toxicology and disease. *Toxicol Sci*. 2009;112:4-16.
30. Yannakoulia M, Karayiannis D, Terzidou M, Kokkevi A, Sidossis LS. Nutrition-related habits of Greek adolescents. *Eur J Clin Nutr*. 2004; 58:580-586.
31. Lawlor DA, Callaway M, Macdonald-Wallis C, et al. Nonalcoholic fatty liver disease, liver fibrosis, and cardiometabolic risk factors in adolescence: a cross-sectional study of 1874 general population adolescents. *J Clin Endocrinol Metab*. 2014;99:E410-E417.
32. VanWagner LB, Khan SS, Ning H, et al. Body mass index trajectories in young adulthood predict non-alcoholic fatty liver disease in middle age: the CARDIA cohort study. *Liver Int*. 2018;38:706-714.
33. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol*. 2012;41: 514-520.
34. Geurtsen ML, Jaddoe VWV, Salas LA, Santos S, Felix JF. Newborn and childhood differential DNA methylation and liver fat in school-age children. *Clin Epigenetics*. 2019;12:3.
35. Liska D, Dufour S, Zern TL, et al. Interethnic differences in muscle, liver and abdominal fat partitioning in obese adolescents. *PLoS One*. 2007;2:e569.
36. Shaw NJ, Crabtree NJ, Kibirige MS, Fordham JN. Ethnic and gender differences in body fat in British schoolchildren as measured by DXA. *Arch Dis Child*. 2007;92:872-875.
37. Staiano AE, Katzmarzyk PT. Ethnic and sex differences in body fat and visceral and subcutaneous adiposity in children and adolescents. *Int J Obes (Lond)*. 2012;36:1261-1269.
38. Kim JW, Lee KJ, Yang HR, et al. Prevalence and risk factors of elevated alanine aminotransferase among Korean adolescents: 2001-2014. *BMC Publ Health*. 2018;18:617.
39. Pirimoglu B, Sade R, Islek A, Kantarci M. The liver fat fraction and abdominal subcutaneous and visceral fat volume distribution in normal-weight, overweight, and obese children using a new magnetic resonance imaging technique. *J Comput Assist Tomogr*. 2019;43: 194-199.
40. Cantoral A, Montoya A, Luna-Villa L, et al. Overweight and obesity status from the prenatal period to adolescence and its association with non-alcoholic fatty liver disease in young adults: cohort study. *BJOG*. 2020;127:1200-1209.
41. Lee S, Kuk JL, Boesch C, Arslanian S. Waist circumference is associated with liver fat in black and white adolescents. *Appl Physiol Nutr Metab*. 2017;42:829-833.
42. Yu EL, Golshan S, Harlow KE, et al. Prevalence of nonalcoholic fatty liver disease in children with obesity. *J Pediatr*. 2019;207:64-70.

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