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Research Article

Association between obesity profile and non-alcoholic fatty liver by race/ethnicity

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Abstract

NAFLD is characterized by accumulation of fat in the liver that can lead to health complications. Previous studies have found the obesity phenotype and its components to be risk factors for the development of NAFLD. This study aims to examine the relationship between the obesity phenotype and NAFLD among each racial-ethnic group. We analyzed data from the NHANES III survey (1988-1994). The obesity phenotype was defined based on BMI and metabolic syndrome. NAFLD was defined by abdominal ultrasounds among non-alcoholics with no infection or taking drugs affecting the liver. A higher prevalence of NAFLD was found among the metabolically unhealthy obese group (43.1%) and the metabolically unhealthy overweight (29.4%) than the metabolically unhealthy normal weight (11.8%). Mexicans-Americans had higher odds of NAFLD relative to whites (adjusted odds ratio (AOR) = 1.3, 95% confidence interval (CI) = 1.01-1.9, p = 0.04). The metabolically healthy obese phenotype was associated with NAFLD (p > 0.05) in the overall sample and in Whites. The metabolically healthy overweight was associated with NAFLD only among Mexican-American (p < 0.05). Metabolically unhealthy overweight or obese had higher odds of NAFLD relative to the metabolically healthy normal weight and this relation is consistent in all the racial/ethnic groups (p < 0.05). Metabolically healthy overweight and obese individuals had a high chance of NAFLD and it varied by race/ethnicity. Healthcare providers should pay more attention to care for those who are part of the metabolically healthy overweight or obese group especially among the Mexican-American population.

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Introduction

Fatty liver disease is typically characterized by resistance to insulin along with fat accumulation in the liver [1,2]. Non-alcoholic fatty liver disease (NAFLD) refers to fatty liver disease that is not related to excessive alcohol consumption, drug consumption, or liver injury caused by herbal products [1,2]. NAFLD is the most common cause of liver disease in the world with a prevalence of about 30% in developed countries [1]. Patients with NAFLD often develop comorbidities that can lead to a bigger burden being placed on the healthcare system. If not treated, NAFLD can develop into NASH which often leads to advance liver disease, hepatocellular carcinoma (HCC), and cirrhosis; consequently, NASH is now considered the second biggest risk factor in determining who needs a liver transplant [3].

NAFLD primarily affects those who are obese, but also affects patients who are lean [4]. Associations have been found between hepatic steatosis and metabolic syndrome and its components, including central obesity based on waist circumference, insulin resistance, dyslipidemia, hypertension, and hypertriglyceridemia [2,5-7]. The prevalence of metabolic syndrome in NAFLD patients in one study was 41.3% [8]. Patients with both metabolic syndrome and NAFLD have also been found to have a higher risk of developing NASH and fibrosis of the liver [1].

The obesity phenotype refers to classification based on metabolic health and obesity. Body mass index (BMI) is typically used to classify obesity [9]. While obesity and metabolic syndrome are highly correlated, some individuals have only one of the risk factors and not the other. Thus, obesity phenotype can ranging from metabolically unhealthy normal weight to metabolically healthy obese [10-12]. A metabolically obese phenotype, for example, would be characterized by elevated body mass index (BMI) and a healthy metabolic profile. There is limited research investigating how obesity phenotype affects risk for NAFLD. Chang, et al. [13] found that in a cohort of metabolically healthy obese individuals, obesity was progressively associated with incidence of NAFLD, while

Shaharyar, et al. [14] found that incidence of hepatic steatosis was higher in metabolically healthy obese subjects compared to metabolically healthy normal weight subjects. On the other hand, in studies of non-obese subjects, increases in the number of diagnosed metabolic components corresponded with increased prevalence of NAFLD [15,16]. These studies highlight the importance of looking at both components of the obesity phenotype to assess risk for NAFLD.

Previous studies have indicated that NAFLD varies by race/ethnicity. Several studies have found higher NAFLD prevalence in Hispanics and lower prevalence in Blacks when compared to non-Hispanic whites [17-19]. A growing literature is showing that genetic risk factors, which are unequally distributed among the different racial/ethnic groups, are associated with the development of NAFLD [20,21]. Studies investigating racial disparities in obesity phenotype are lacking. However, a recent study by the Center for Disease Control and Prevention (CDC) has shown the highest prevalence of obesity to occur in non-Hispanic Blacks, followed by Hispanics [22]. Previous studies have also observed differences in the prevalence of metabolic syndrome in Hispanics compared to other groups, but results have been more mixed and strongly impacted by sex [23-25].

This study's aim was to examine the relationship between the obesity phenotype and the prevalence of NAFLD in the United States population among each racial/ethnic group. We used data from Third National Health and Nutrition Examination Survey (NHANES III). While these data were collected several years ago, they remain important because they constitute a nationally representative sample of the U.S. population and use ultrasound for the diagnosis of liver steatosis. It is imperative that medical providers are aware of how obesity phenotype affects the risk for liver disease, and particularly how this risk factor differs between racial/ethnic groups so that they can screen and monitor patients appropriately.

We hypothesized that metabolically healthy overweight/obese individuals will be more likely to have NAFLD relative to the metabolically healthy normal weight individuals. In addition, this relation is more likely to occur in Mexican-Americans relative to Whites.

Materials and methods

Data source

We analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III) 1988-1994 which is a cross-sectional survey using multistage stratified sample of a representative sample of the non-institutionalized population of the United States to examine the health and nutrition of children and adults.

The survey protocol was approved by the NCHS Research Ethics Review Board and was in accordance with the Declaration of Helsinki [26]. Informed consent was obtained from all participants prior to participation. The details of the NHANES III procedures can be found in the article that included the program and collections procedure as well as the plan and operation of the study [27].

The Third NHANES study took place over 6 years and involved 33,994 participants aged 2 months and older. Initial interviews were completed at the participants' residences, while physical and laboratory examinations were conducted at mobile examination centers [27]. NHANES III oversampled Mexican Americans, non-Hispanic blacks, persons 60 years and older, and children ages two months to five years. We analyzed data from NHANES III for adults aged 20 years and older with ultrasound data.

Main independent variables

The independent variables for this study are the obesity phenotype and race/ethnicity. Obesity phenotype was categorized by BMI and metabolic syndrome, creating six levels: metabolically healthy normal weight; metabolically healthy overweight; metabolically healthy obese; metabolically unhealthy normal weight; metabolically unhealthy overweight; metabolically unhealthy obese. Obesity classification was defined as follows: Normal weight BMI $< 25\ kg/m^2$, overweight BMI ≥ 25 and $< 30\ kg/m^2$ and obese BMI $\geq 30\ kg/m^2$. Metabolically healthy was defined as having 1 or fewer components of metabolic syndrome, while unhealthy was having more than 1 component. The components considered were: 1) Systolic blood pressure (SBP ≥ 140 mm-Hg) and/or diastolic blood pressure (DBP ≥ 90 mm-Hg) or current drug treatment for hypertension. 2) Waist circumference > 88 cm for women, >102 cm for men. 3) Fasting plasma glucose ≥100 mg/dl (5.6 mmol/l) or current drug treatment for diabetes. 4) HDL < 50 mg/dl (1.29 mmol/l) for women, < 40 mg/dl (1.03 mmol/l) for men or current drug treatment for high cholesterol. 5) Fasting triglycerides ≥ 150 mg/dl (1.7 mmol/l) or current drug treatment for high triglycerides. Race and ethnicity were grouped into the following categories: non-Hispanic white, non-Hispanic Black, Mexican American, or other.

Dependent variable

The dependent variable for this study was NAFLD. Participants 20 years and older in the NHANES III underwent abdominal ultrasonography. In NHANES III, the ultrasound recordings were analyzed and subjects were rated as having no, mild, moderate, or severe hepatic steatosis. For the purposes of our study, cases with moderate to severe steatosis were classified as having hepatic steatosis. Participants were considered to have NAFLD if they had hepatic steatosis and did not have any exclusion criteria. Exclusion criteria included elevated transferrin level >50%, chronic hepatitis B, chronic hepatitis C, excessive alcohol use, or prescription medications that might cause hepatic steatosis [28-30]. Chronic hepatitis B

was defined as positive results for both the hepatitis B surface antigen and hepatitis B core antibody tests. Chronic hepatitis C was defined as positive results for both the hepatitis C antibody and RNA tests. Excessive alcohol use was defined as an average of more than 2 drinks/day for men or 1 drink/day for women. Average alcohol use was determined by multiplying the responses to the two questions: "Number of days drank alcohol in past 12 months" and "average drinks per day on drinking day" and dividing by 365 to get a daily average.

Confounding variables

We included potential confounding factors for hepatic steatosis and NAFLD based on literature review. The following variables were included in the analyses: demographics (age, sex, education, urbanization, and poverty), physical activity status, smoking status, laboratory values (cholesterol, HbA1c, HOMA insulin resistance (IR), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and C-peptide), hypertension and healthy eating index (HEI).

Age was measured in years in NHANES III. Sex was recorded as either female or male. Education level was categorized as less than the 12th grade, completed 12th grade, and completed past the 12th grade. Language spoken at home was classified as English, Spanish, both English and Spanish, or other. Alcohol consumption by participants was recorded as never, former, and current.

Urbanization was classified as urban if the subject lived in a metro area containing at least 1 million people, and rural otherwise. Federal poverty ratio was defined as the family income divided by the federal poverty threshold and classified as <1, 1-2, and >2. Physical activity was assessed by asking subjects how often they engaged in a variety of recreational or other activities requiring physical exertion. Subjects who reported not doing any of the activities were classified as inactive. National guidelines at the time of data collection recommended doing moderate activity at least 5 times/week or vigorous activity at least 3 times/week. We further classified active subjects based on these guidelines into active & meets guidelines and active & does not meet guidelines. Smoking was classified as never, former, or current. C-peptide levels were classified as low (< 0.26 nmol/L), normal (0.26-1.03 nmol/L), and high (>1.03 nmol/L). Total cholesterol was categorized as normal (≤ 200 mg/dL), elevated (200-239 mg/dL), and high (≥ 240 mg/dL). Triglyceride levels were categorized as normal (< 150 mg/dL), borderline (150-190 mg/dL), or high (≥ 200 mg/dL). Glucose was categorized as normal (< 100 mg/dL), prediabetes (100-125 mg/dL), or diabetes (> 125 mg/dL). ALT was categorized as normal (≤ 56 U/L) or elevated > 56 U/L). AST was categorized as normal (≤ 40 U/L) or elevated > 40 U/L). CRP was categorized as normal (0.1 - < 0.3 mg/dL), mild (mild inflammation) (0.3-1 mg/dL), and high (significant inflammation) (> 1 mg/dL).

Statistical analysis

The main independent variables in this study were obesity phenotype and race/ethnicity. The dependent variable was NAFLD. Population characteristics are presented using descriptive statistics. Categorical variables are presented as unweighted numbers and weighted percent. We examined the differences in population characteristics and NAFLD outcome by the independent variables using Chi-square tests. We used multiple logistic regression to determine the relationship between the obesity phenotype and NAFLD status for each racial/ethnic group and adjusted for the other independent variables. We present the data as adjusted odds ratio and 95% confidence interval and p-value of < 0.05 is considered statistically significant. We analyzed the data using SAS (Release V.9.1.3, 2002; SAS, Inc) and the survey module of STATA (Release V.10, 1984e2007 Statistics/Data Analysis; StataCorp). The NCHS provided sample weights that we used to correct for differential selection probabilities and to adjust for non-coverage and non-response. All estimates were weighted as supplied by NHANES and the design has been taken into consideration.

Results

Population characteristics

We analyzed data from 13,060 people who participated in NHANES III. Table 1 shows the population characteristics. The largest groups was metabolically healthy normal weight (36.3%). The metabolically healthy obese represented 3.9%; 19.1% were metabolically unhealthy obese, 7.9% were metabolically unhealthy normal weight, 17.5% were metabolically unhealthy overweight, and 15.3% were metabolically healthy overweight.

Most of the participants were White (75.5%) followed by a smaller percentage of Blacks (11%) and Mexican-Americans (5.5%). Mexican-Americans had the highest prevalence of metabolically healthy overweight (18.9%) compared to Whites (14.9%) and Blacks (17.7%). Mexican-Americans had a higher prevalence of metabolically unhealthy overweight (19%) when compared to Whites (18%) and Blacks (14.7%). Blacks had the highest prevalence of metabolically healthy obese (7.5%) when compared to Whites (3.4%) and Mexican-Americans (3.8%). Blacks also had a higher prevalence of the metabolically unhealthy obese (23.3%) when compared to Whites (18.5%) and Mexicans (23.2%).

Prevalence of NAFLD

The prevalence of NAFLD in the population was 18.5%. The highest prevalence of NAFLD was found in the metabolic unhealthy obese group (43%), followed by 29.4% among the metabolic unhealthy overweight group, and 18.5% among the metabolic healthy ($p < 0.05$). NAFLD prevalence was also found to be higher in Mexican-Americans (25.5%) compared to whites (17.8%), and lowest in Blacks (14.7%).

Table 1: Overall population characteristics and by non-alcoholic fatty liver status.

Variables	Total		NAFLD (*n* = 2790, 8.5%)		Normal/Mild Steatosis (*n* = 10745, 81.7%)		*p* - value
	Number	Weighted percent	Number	Weighted Percent	Number	Weighted Percent	
Obesity Phenotype							0.0001
Metabolically healthy normal weight	3976	36.3	307	6.2	3606	93.8	
Metabolically healthy overweight	2003	15.3	236	8	1727	92	
Metabolically healthy obese	585	3.9	103	18.5	472	81.5	
Metabolically unhealthy normal weight	1062	7.9	158	11.8	877	88.2	
Metabolically unhealthy overweight	2532	17.5	695	29.4	1750	70.6	
Metabolically unhealthy obese	2998	19.1	1199	43.1	1668	56.9	
Age (years)							0.0001
20-34	5024	37.23	656	11.6	4284	88.4	
35-49	3958	32.33	843	17.9	2989	82.1	
50+	4928	30.44	1291	26	3472	74	
Race/Ethnicity							0.0001
White	5068	75.53	979	17.8	3961	82.2	
Black	4094	10.98	622	14.7	3388	85.3	
Mexican-American	4164	5.48	1085	25.5	2930	74.5	
Other	584	8.01	104	18.6	466	81.4	
Sex							0.0009
Male	6508	48.48	1365	19.6	4889	80.4	
Female	7402	51.52	1425	16.4	5856	83.6	
Urban/rural							0.009
Urban	7051	48.76	1303	16.1	5552	83.9	
Rural	6859	51.24	1487	19.7	5193	80.2	
Language spoken at home							0.0005
English	11000	89.39	1969	17.8	8358	82.2	
Spanish	2795	6.262	727	24.2	1975	75.9	
Both	323	4.012	48	16.9	135	83.1	
Other	194	0.3342	46	12.1	275	87.9	
Federal poverty level							0.3346
< 1	3434	20.39	666	19.9	2256	80.1	
1 to 2	3022	12.61	696	18.9	2630	81.1	
> 2	6238	66.99	1157	17.3	4946	82.7	
Smoking status							0.0001
Current	3951	29.79	612	13.8	3183	86.2	
Former	3195	24.94	817	24.2	2263	75.8	
Non-smoker	6763	45.26	1361	17.3	5298	82.7	
Physical activity							0.0001
Inactive	3107	15.62	748	22.1	2260	77.9	
Does not meet guideline	5488	40.6	1162	19.6	4178	80.4	
Meets guidelines	5315	43.77	880	14.9	4307	85.1	
Education grade completed							0.0001
less than high school	4406	34.45	1318	22.8	3818	77.2	
high school	5329	23.28	814	18.8	3482	81.2	
more than high school	4086	42.27	644	14.7	3373	85.3	
Total cholesterol							0.0001
good (< 200 mg/dL)	6544	50.15	1063	13.8	5321	86.2	
elevated (200-239 mg/dL)	4172	31.13	960	20.5	3099	79.6	
high (> = 240 mg/dL)	2566	18.72	655	25.2	1820	74.8	
Triglyceride							0.0001
normal (< 150 mg/dL)	8998	68.89	1223	10.7	7573	89.3	
borderline (150-199 mg/dL)	2397	17.59	511	26	1288	74	
high (> = 200 mg/dL)	1854	13.52	942	41.1	1349	58.6	
C-reactive protein (CRP)							0.0001
normal (0.1 - < 0.3 mg/dL)	8766	72.45	1448	15	7112	85	
mild inflammation (0.3-1 mg/dL)	3302	21	925	26.3	2261	73.7	
significant inflammation (> 1 mg/dL)	1138	6.54	291	26.4	805	73.6	
Serum glucose							0.0001
normal (< 100 mg/dL)	9625	77.22	1512	14.1	7905	85.9	
prediabetes (100-125 mg/dL)	972	4.83	698	26.8	1778	73.2	
diabetes (> 125 mg/dL)	2579	17.96	439	51.4	437	48.6	
Aspartate amino transferase (AST)							0.0001
normal (< = 40 U/L)	12000	96.3	2441	17.5	9784	82.5	
elevated (> 40 U/L)	655	3.7	210	36.6	338	63.4	
Alanine amino transferase (ALT)							0.0001

normal (< = 56 U/L)	13000	97.8	2511	17.5	9941	82.5	
elevated (> 56 U/L)	385	2.203	140	46	181	54	
Healthy eating index score (HEI)							
poor diet (< 50)	1323	10.86	462	17.8	1842	82.2	
needs improvement (50-80)	9814	73.37	1984	17.8	7551	82.2	
good diet (80-100)	2367	15.77	276	19.5	1026	80.5	
Hypertension							0.0001
Yes	3720	21.9	1081	30.5	2480	69.5	
No	10000	78.1	1686	14.6	8147	85.4	
C-peptide							0.0001
low (< 0.26 nmol/L)	1760	14.99	104	4.6	1624	95.4	
normal (0.26-1.03 nmol/L)	8578	66.36	1339	13.6	7068	86.4	
high (> 1.03 nmol/L)	3010	18.65	1242	45.4	1604	54.6	

Multiple logistic regression analysis

Table 2 shows the multiple logistic regression analysis of NAFLD and obesity phenotype after adjustment for confounding variables and table 3 shows the stratified analysis by race/ethnicity. The overall results of the multiple logistic regression analysis adjusting for the confounding variables indicated that Mexican-Americans had a greater odds of having NAFLD than whites (AOR = 1.38, 95% CI = 1.01-1.9, $p = 0.04$), and while Blacks had a lower chance of NAFLD than whites, the difference was not statistically signficant. Compared to the metabolically healthy normal weight, the metabolically unhealthy obese adults had the highest odds of NAFLD (AOR = 3.85, 95% CI = 2.79-5.31, $p < .0001$), followed by the metabolically healthy obese (AOR = 2.68, 95% CI = 1.51-4.8, $p = .001$) and the metabolically unhealthy overweight (AOR = 2.5, 95% CI = 1.86-3.37, $p = <.0001$).

Whites showed a relationship between obesity phenotype and NAFLD that was consistent to the overall pattern, where compared with the metabolically healthy normal weight, the highest odds of NAFLD were in the unhealthy obese group (AOR = 4.14, 95% CI = 2.78-6.16, $p = <.0001$), followed by the healthy obese (AOR = 3.31, 95% CI = 1.48-7.41, $p = .004$) and the unhealthy overweight (AOR = 2.75, 95% CI = 1.92-3.93, $p = < 0.0001$).

For Blacks, the only group that had a significantly elevated risk of NAFLD compared to the metabolically healthy normal weight were the metabolically unhealthy obese (AOR = 1.86, 95% CI = 1.32-2.63, $p = .001$). Most other groups actually had a reduced risk of NAFLD, but none of these differences were statisically significant.

In Mexican-Americans, compared to the healthy normal weight group, all other obesity phenotypes had increased odds of NAFLD, although these differences were not statistically significant for the metabolically unhealthy normal weight or the metabolically healthy obese. The largest odds was in the metabolically unhealthy obese (AOR = 3.85, 95% CI = 2.33-6.38, $p = <.0001$), followed by the metabolically unhealthy overweight (AOR = 2.06, 95% CI = 1.37-3.09, $p = 0.001$) and the metabolically healthy overweight (AOR = 1.52, 95% CI = 1.14-2.03, $p = 0.005$).

The confounding variables showed consistent effects across the racial/ethnic groups except for sex and age. Overall, females were less likely to have NAFLD than males (AOR = .82, 95% CI = .70-.97, $p = .021$), and the risk for NAFLD increased in older age groups, with a significant difference in the 50+ group compared to those 20-34 (AOR = 1.40, 95% CI = 1.08-1.82, $p = 0.012$). When stratified by racial/ethnic group, only Mexican-Americans showed significantly lower odds in females compared to males (AOR = .69, 95% CI = .53-.89, $p = .006$). Similarly, only in Mexican-Americans did those in the 35-49 group (AOR = 1.58, 95% CI = 1.18-2.13, $p = 0.003$) and 50+ group (AOR = 1.42, 95% CI= 1.02-1.97, $p = 0.038$) have higher odds of NAFLD than those in the 20-34 group.

Discussion

The purpose of this study was to examine the relationship between the obesity phenotype and NAFLD in each racial/ethnic group in the US population. In the overall population, we found an independent association between the obesity phenotype and NAFLD where metabolically healthy and unhealthy obese individuals had a higher chance of NAFLD relative to metabolically healthy normal weight individuals. This finding is consistent with previous work that has found that metabolically healthy and metabolically abnormal obese individuals are both at high risk for hepatic steatosis [31,32]. We also found that metabolically unhealthy overweight individuals had a higher chance of NAFLD compared to the metabolically healthy normal weight, showing the importance of normal weight maintenance and metabolic health. Together, these results indicate that neither component of the obesity phenotype alone is sufficient to determine risk for NAFLD, but that the entire obesity phenotype must be considered.

Mexican-Americans had the highest prevalence of NAFLD, while Blacks had the lowest. We saw consistently higher odds of NAFLD in the metabolically unhealthy obese group relative to the metabolically healthy normal weight in all racial/ethnic groups. Among the Black population, none of the other obesity phenotypes increased risk for NAFLD. Both whites and Hispanics had increased odds of NAFLD in the metabolically unhealthy overweight group compared to the metabolically healthy normal weight group. However, only whites had increased odds of NAFLD in the metabolically healthy obese

Table 2: Adjusted odds ratio and 95% confidence intervals for significant associations with NAFLD based on multiple logistic regression

Outcome: non-alcoholic fatty liver	Adjusted Odds Ratio	Lower 95% Confidence level	Upper 95% confidence level	*p* - value
Obesity phenotype				
Metabolically healthy overweight versus metabolically healthy normal weight	1.05	0.71	1.53	0.812
Metabolically healthy obese versus metabolically healthy normal weight	2.68	1.51	4.75	0.001
Metabolically unhealthy normal weight versus metabolically healthy normal weight	1.01	0.71	1.42	0.971
Metabolically unhealthy overweight versus metabolically healthy normal weight	2.50	1.86	3.37	< 0.0001
Metabolically unhealthy obese versus metabolically healthy normal weight	3.85	2.79	5.31	< 0.0001
Female versus male	0.82	0.70	0.97	0.021
Race/ethnicity				
Black versus white	0.84	0.66	1.07	0.151
Mexican-American versus white	1.38	1.01	1.90	0.044
Other versus white	1.38	0.86	2.22	0.18
Rural versus urban	1.18	0.96	1.44	0.106
Language spoken at home				
Spanish versus English	0.97	0.70	1.35	0.856
Both English and Spanish versus English	0.60	0.34	1.04	0.067
Other versus English	0.56	0.25	1.25	0.154
Smoking status				
Current versus never	0.67	0.55	0.82	< 0.0001
Former versus never	1.10	0.88	1.36	0.388
Age group (years)				
35-49 versus 20-34 years	1.21	0.94	1.54	0.129
50+ versus 20-34 years	1.40	1.08	1.82	0.012
Healthy eating index group				
needs improvement versus good	1.05	0.83	1.32	0.699
poor diet versus good	1.09	0.75	1.57	0.641
Cholesterol groups				
elevated (200-239 mg) versus normal	0.88	0.76	1.02	0.097
high (> = 240 mg/dL) versus normal	0.82	0.64	1.06	0.123
Triglyceride groups				
borderline (150-199) versus normal	1.44	1.12	1.85	0.005
high (> = 200 mg/dL) versus normal	2.27	1.85	2.78	< 0.0001
Glucose groups				
diabetes (> 125 mg/dL) versus normal	2.14	1.61	2.85	< 0.0001
prediabetes (100-125) versus normal	1.06	0.86	1.30	0.604
ALT groups				
elevated (> 56 U/L) versus normal	2.26	1.08	4.75	0.032
AST groups				
elevated (> 40 U/L) versus normal	1.41	0.82	2.43	0.213
Education level				
high school versus more than high school	1.13	0.95	1.33	0.156
less than high school versus more than high school	1.12	0.94	1.33	0.187
CRP groups				
mild inflammation versus normal	1.17	0.96	1.44	0.115
significant inflammation versus normal	0.87	0.68	1.13	0.297
C-peptide groups				
high (>1.03 nmol/L) versus normal	2.10	1.73	2.54	< 0.0001
low (<.26 nmol/L) versus normal	0.57	0.41	0.79	0.001
Hypertension				
yes versus no	0.97	0.78	1.22	0.795
Poverty ratio				
1 to 2 versus > 2	1.03	0.81	1.31	0.798
< 1 versus > 2	0.97	0.76	1.23	0.777
Physical activity				
inactive versus active & meets guidelines	1.18	0.93	1.49	0.174
Active & does not meet guidelines versus active & meets guidelines	1.06	0.89	1.26	0.533

Table 3: Adjusted odds ratio and 95% confident intervals for significant associations with NAFLD based on multiple logistic regression for each racial/ethnic group.

	White				Black				Mexican-American			
Outcome: non alcoholic fatty liver	Adjusted Odds Ratio	Lower 95% Confidence level	Upper 95% confidence level	*p* - value	Adjusted Odds Ratio	Lower 95% Confidence level	Upper 95% confidence level	*p* - value	Adjusted Odds Ratio	Lower 95% Confidence level	Upper 95% confidence level	*p* - value
Obesity phenotype												
Metabolically healthy overweight versus metabolically healthy normal weight	1.04	0.62	1.75	0.885	0.94	0.64	1.37	0.724	1.52	1.14	2.03	0.005
Metabolically healthy obese versus metabolically healthy normal weight	3.31	1.48	7.41	0.004	1.25	0.72	2.15	0.422	1.59	0.88	2.88	0.123
Metabolically unhealthy normal weight versus metabolically healthy normal weight	0.99	0.68	1.43	0.953	0.61	0.36	1.02	0.057	1.67	0.90	3.09	0.101
Metabolically unhealthy overweight versus metabolically healthy normal weight	2.75	1.92	3.93	0.0001	0.87	0.57	1.33	0.511	2.06	1.37	3.09	0.001
Metabolically unhealthy obese versus metabolically healthy normal weight	4.14	2.78	6.16	0.0001	1.86	1.32	2.63	0.001	3.85	2.33	6.38	0.0001
Female versus male	0.89	0.74	1.07	0.212	0.86	0.60	1.23	0.408	0.69	0.53	0.89	0.006
Rural versus urban	1.18	0.92	1.51	0.178	1.25	0.83	1.88	0.282	1.14	0.74	1.75	0.553
Language spoken at home												
Spanish versus English	0.78	0.10	6.22	0.81	0.75	0.14	3.93	0.731	1.05	0.77	1.44	0.755
Both English and Spanish versus English	0.51	0.21	1.26	0.142	0.53	0.15	1.96	0.334	2.14	0.75	6.08	0.148
Other versus English	1.00				1.00				1.06	0.66	1.70	0.815
Smoking status												
Current versus never	0.68	0.53	0.86	0.002	0.65	0.49	0.87	0.005	0.66	0.49	0.90	0.01
Former versus never	1.11	0.86	1.44	0.416	0.95	0.69	1.31	0.756	1.12	0.89	1.40	0.324
Age group (years)												
35-49 versus 20-34 years	1.18	0.86	1.61	0.302	1.07	0.79	1.45	0.667	1.58	1.18	2.13	0.003
50+ versus 20-34 years	1.36	0.98	1.91	0.069	1.26	0.87	1.81	0.212	1.42	1.02	1.97	0.038
Healthy eating index group												
needs improvement versus good	1.06	0.81	1.39	0.672	1.61	0.93	2.80	0.088	1.10	0.83	1.45	0.498
poor diet versus good	1.14	0.72	1.80	0.573	1.78	0.93	3.39	0.081	0.94	0.70	1.27	0.677
Cholesterol groups												
elevated (200-239 mg) versus normal	0.83	0.68	1.00	0.049	1.22	0.93	1.59	0.149	0.95	0.73	1.24	0.695
high (>=240 mg/dL) versus normal	0.77	0.58	1.02	0.071	1.36	0.96	1.92	0.08	0.99	0.78	1.25	0.912
Triglyceride groups												
borderline (150-199) versus normal	1.56	1.14	2.14	0.007	1.33	0.89	1.98	0.156	1.16	0.75	1.81	0.495
high (>=200 mg/dL) versus normal	2.28	1.79	2.91	<0.0001	1.86	1.29	2.67	0.001	1.39	1.03	1.88	0.034
Glucose groups												
diabetes (>125 mg/dL) versus normal	2.19	1.52	3.16	<0.0001	2.02	1.31	3.09	0.002	2.20	1.51	3.20	<0.0001
prediabetes (100-125) versus normal	0.95	0.73	1.25	0.729	1.16	0.86	1.55	0.326	1.29	0.91	1.82	0.155
ALT groups												
elevated (>56 U/L) versus normal	2.82	0.92	8.66	0.069	0.82	0.26	2.63	0.733	2.06	1.28	3.33	0.004
AST groups												
elevated (>40 U/L) versus normal	1.50	0.70	3.25	0.292	1.56	0.87	2.80	0.129	1.51	0.89	2.58	0.123
Education level												
high school versus more than high school	1.10	0.90	1.36	0.339	1.04	0.81	1.34	0.736	0.98	0.66	1.47	0.936
less than high school versus more than high school	1.10	0.86	1.41	0.45	1.18	0.84	1.65	0.335	0.99	0.70	1.39	0.952
CRP groups												
mild inflammation versus normal	1.15	0.87	1.51	0.321	1.24	0.96	1.60	0.091	1.22	0.97	1.54	0.083
significant inflammation versus normal	0.85	0.62	1.15	0.283	1.10	0.79	1.53	0.569	0.75	0.54	1.04	0.084
C-peptide groups												
high (>1.03 nmol/L) versus normal	2.20	1.72	2.81	<0.0001	1.87	1.44	2.44	<0.0001	1.93	1.40	2.65	<0.0001
low (<.26 nmol/L) versus normal	0.52	0.35	0.76	0.001	0.70	0.46	1.06	0.093	0.41	0.22	0.79	0.009
Hypertension												
yes versus no	1.06	0.83	1.36	0.625	1.02	0.73	1.43	0.901	1.00	0.71	1.40	0.99
Poverty ratio												
1 to 2 versus >2	0.96	0.69	1.34	0.815	1.10	0.75	1.62	0.616	1.21	0.89	1.64	0.215
<1 versus >2	0.94	0.64	1.37	0.733	1.09	0.78	1.53	0.61	1.14	0.81	1.61	0.455
Physical activity												
inactive versus active & meets guidelines	1.24	0.90	1.71	0.187	1.04	0.76	1.42	0.813	1.11	0.82	1.51	0.496
Active & does not meet guidelines versus active & meets guidelines	1.04	0.84	1.29	0.694	1.18	0.85	1.62	0.31	1.00	0.84	1.18	0.964

group, while only Hispanics had increased odds of NAFLD in the metabolically healthy overweight group. These results highlight the importance of considering racial/ethnic group in how the obesity phenotype affects risk for NAFLD.

Previous studies have not evaluated race/ethnicity as a factor in the relationship between obesity phenotype and hepatic steatosis. However, other studies have tended to find that NAFLD prevalence is highest in Hispanics and lowest in Blacks [18,20]. Various factors are thought to account for racial/ethnic differences in risk for and prognosis of NAFLD, including differences in socio-economic status and access to care [20]. Genetic factors, in particular, are thought to have a major influence on risk and severity. For example, polymorphisms of *PNPLA3*, *TM6SF2*, and *MBOAT* are associated with risk for NAFLD and are distributed unequally among different racial/ethnic groups, providing potential mechanisms for the observed racial disparities [20,21]. Additionally, one study found that a certain polymorphism of *PNPLA3* seems to be more involved in progression of NAFLD in non-obese individuals than obese individuals [33], while another study found that carriers of the polymorphism were less likely to have metabolic syndrome [34]. In another study, while metabolic syndrome was associated with an increased risk of NAFLD-related mortality, polymorphisms of *PNPLA3*, *TM6SF2*, and *MBOAT* were not [35]. The interactions between these genetic factors may provide a potential mechanism for interaction between the effects of race/ethnicity and obesity phenotype on risk for NAFLD. Further research is needed to illuminate the mechanism underlying this interaction.

Limitations

Our study had some limitations. First, hepatic steatosis data from NHANES III (1988-1994) were based on ultrasound files. The sensitivity, specificity, and accuracy of ultrasound has been shown to be 85%, 94%, and 93% when compared to liver biopsy [36]. In regards to diagnoses made through imaging, the literature has established that imaging tests such as ultrasounds and CT scans are unable to differentiate between hepatic fibrosis from simple hepatic steatosis as seen in patients with NAFLD [2]. Ultrasonography has also been criticized for low sensitivity to mild steatosis and poor discrimination between moderate and severe steatosis, but since our steatosis definition did not include mild levels and combined moderate and severe, these concerns would not affect our results. Newer methods such as transient liver elastography can differentiate between hepatic steatosis and hepatic fibrosis with better accuracy than ultrasound. But NHANES III remains the only nationally representative sample that allows for identification of NAFLD. A related limitation is that because of the way we categorized steatosis groups, we did not assess degree of severity of hepatic steatosis or fibrosis.

A second limitation was how the obesity phenotype was defined in this study. There is no universal definition for this phenotype. As a result, other definitions might have resulted in different outcomes. While the metabolic syndrome has a more consistent definition, there may still be some differences in the various cutoffs used. It is well known that a variety of factors exist amongst different ethnic groups which can determine metabolic health and can involve other markers not addressed in this study.

A third limitation is that the survey design was cross-sectional study so we cannot make causal inference and determine the mechanism of the association. We can only determine an association between NAFLD and the obesity phenotype. Furthermore, some of the variables were measured by self-report where there is a possibility of recall bias.

Conclusion

This study shows that an independent relationship exists between the obesity phenotype and NAFLD. The metabolically healthy obese had a high chance of NAFLD. The odds of NAFLD were higher in those who are part of the metabolically unhealthy overweight and obese groups compared to those in the metabolically healthy normal group. Furthermore, there were differences by race/ethnicity. The prevalence of NAFLD was highest in Mexican-Americans when compared to Whites. Also, only in Mexican-Americans, the metabolic healthy overweight groups had a higher chance of developing NAFLD. These findings support the hypothesis that the prevalence of NAFLD is higher among the metabolically healthy overweight and obese phenotypes in the US population.

Recommendations

Therefore, healthcare providers should pay more attention to care for those who are part of the metabolically healthy overweight or obese group, especially among the Mexican-American population. We recommend further research to explore the possible mechanism of the relation between NAFLD and obesity phenotype.

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