6-2017

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## Recommended Citation

Gill, C., Vatcheva, K. P., Pan, J.-J., Smulevitz, B., McPherson, D. D., Fallon, M., McCormick, J. B., Fisher-Hoch, S. P., & Laing, S. T. (2017). Frequency of Nonalcoholic Fatty Liver Disease and Subclinical Atherosclerosis Among Young Mexican Americans. The American Journal of Cardiology, 119(11), 1717–1722. https://doi.org/10.1016/j.amjcard.2017.03.010

HHS Public Access

Author manuscript

*Am J Cardiol*. Author manuscript; available in PMC 2018 September 11.

Published in final edited form as:

*Am J Cardiol*. 2017 June 01; 119(11): 1717–1722. doi:10.1016/j.amjcard.2017.03.010.

# Frequency of Nonalcoholic Fatty Liver Disease and Subclinical Atherosclerosis Among Young Mexican Americans

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## Abstract

Non-alcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of the metabolic syndrome, whose criteria are risk factors for atherosclerotic cardiovascular disease. We aimed to evaluate the prevalence of NAFLD, its association with subclinical atherosclerosis, and factors that may account for this association in Mexican Americans. In a population based cross-sectional sample drawn from the Cameron County Hispanic Cohort in Texas, carotid intima media thickness (cIMT), an indicator of subclinical atherosclerosis, was measured. Abnormal carotid ultrasound study was defined as mean cIMT >75$^{th}$ percentile for age and gender and/or plaque presence. NAFLD was defined as steatosis by ultrasound in absence of other causes of liver disease. Multivariable weighted regression analyses were performed to evaluate associations between NAFLD and cIMT. Mean age was 50.4±1.2 years with 58.3% females. Mean body mass index (BMI) was 31.0 ± 0.4 kg/m$^2$, and 54.0% had the metabolic syndrome. NAFLD was highly prevalent (48.80%); subjects with NAFLD had greater BMI, central obesity, fasting glucose levels, and dyslipidemia, and were more likely to have the metabolic syndrome. Nearly one third of subjects with NAFLD also had evidence of subclinical atherosclerosis (31.2%). After adjusting for covariates, there was an independent association between NAFLD and increased cIMT only in younger subjects <45 years (p=0.0328). Subjects with both abnormal liver and carotid ultrasound studies tended to be obese, diabetic, and have the metabolic syndrome. In conclusion, NAFLD is highly prevalent in this Mexican American cohort, with an independent association between NAFLD and subclinical atherosclerosis among younger subjects; clustering of diabetes, obesity,

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and metabolic syndrome in this health disparity cohort increases the risk of both liver disease and early atherosclerosis in young adults.

**Keywords**

Subclinical atherosclerosis; Fatty liver; Minority population; Metabolic Syndrome

Non-alcoholic fatty liver disease (NAFLD), a comprehensive term used to describe a spectrum of metabolic fatty liver diseases, is the most common cause of chronic liver disease in the United States.[1] NAFLD is considered to be the hepatic manifestation of the metabolic syndrome, whose criteria of central (truncal) obesity, hypertriglyceridemia, hypertension, decreased high-density lipoprotein cholesterol, and insulin resistance are also important risk factors for the development of atherosclerotic heart disease.[2–3] Indeed, cardiovascular disease accounts for 25% of deaths in patients with NAFLD versus 13% of deaths in patients with other liver diseases.[4] Although some investigations have shown a relationship between NAFLD and coronary artery disease independent of other metabolic risk factors,[5] other studies have shown inconsistent results[6–7] with relatively little known about the association in minority groups.[8] Hispanics and Latinos face a disparately increased prevalence of coronary risk factors,[9] and in particular, the metabolic syndrome has been shown to be higher in Hispanics than in non-Hispanics.[10] Similarly, NAFLD afflicts Mexican Americans much more than non-Hispanic Whites and non-Hispanic Blacks (25% vs. 18% and 15%, respectively).[11–12] This study aimed to evaluate the prevalence of NAFLD, its association with subclinical atherosclerosis, and the factors that may account for this association in Mexican Americans.

## METHODS

The Institutional Review Board of the University of Texas Health Science Center at Houston approved this study with all participants giving written informed consent. Study subjects were drawn from the Cameron County Hispanic Cohort (CCHC), recruited from randomly selected blocks according to the 2000 Census as described previously.[13] The CCHC is a homogenous community-dwelling Mexican American cohort living in Brownsville, Texas, located on the lower Rio Grande River at the United States-Mexico border. Participants for this study (n=407) were a subset of individuals drawn from the CCHC, on whom we had obtained both a carotid ultrasound to assess carotid intima media thickness (cIMT) and liver ultrasound to evaluate for fatty liver.

Bilingual research nurses and field workers obtained demographics of the participants including an extensive medical history as described in previous studies.[13–14] Participants with a documented history of prior heart attack or stroke were excluded from the study. Anthropometric measurements were obtained including height, weight, and waist circumference. The presence of hypertension was diagnosed using both questionnaires and obtained sphygmomanometer measurements. The subject was deemed to have hypertension if the patient self-reported a prior diagnosis of hypertension, was currently taking anti-hypertensive medications, or if his/her mean systolic blood pressure was ≥130 millimeters of mercury (mm Hg) or the mean diastolic blood pressure was ≥85 mm Hg. Participants were

asked to fast for at least 10 hours overnight before a visit to the Clinical Research Unit. Laboratory studies performed included electrolytes, fasting lipid panel, hepatitis B and C status, complete blood count, glycated hemoglobin, fasting plasma glucose, and adipokines. High-sensitivity C-reactive protein levels were measured using a high-sensitivity immunoassay (Dimension Vista 1500; Siemens Corporation, Washington, DC). High-sensitivity C-reactive protein levels >10 milligrams/liter were excluded from analysis as such high levels likely represent acute illness.[15] Metabolic syndrome was defined as the presence of at least 3 of the following risk factors: 1) elevated waist circumference (≥102 centimeters in males and ≥88 centimeters in females), 2) elevated triglyceride (≥150 milligrams/deciliter) or treatment with triglyceride lowering medication, 3) low high density lipoprotein cholesterol (<40 milligrams/deciliter in males and <50 milligrams/deciliter in females) or treatment with high-density lipoprotein cholesterol raising medication, 4) elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg) or treatment with an anti-hypertensive medication, and 5) elevated fasting glucose (≥100 milligrams/deciliter) or treatment with glucose lowering medication.[16] Classification of diabetes was also both self-reported and based on measurement of hemoglobin A1C (hemoglobin A1C >6.5) as per the latest guidelines from the American Diabetes Association.[17] Physical activity was assessed using the International Physical Activity Questionnaire short-form (IPAQ);[18] reported minutes of physical activity per week were weighted by a metabolic equivalent (MET; multiples of resting energy expenditure) resulting in a physical activity estimate expressed as MET-minutes per week.[18]

Any individual who tested positive for hepatitis C antibody, hepatitis B surface antigen, females with a self-reported history of ≥20 grams of alcohol per day, and males with a self-reported history of ≥30 grams of alcohol per day were excluded from this study. Liver ultrasound was performed using an established protocol.[19] Study participants were asked to fast for at least 8 hours prior to the ultrasound examination. During the scan, liver parenchyma was examined both subcostally and intercostally in the supine position as well as in modified slightly oblique positions with the right arm above the head and the right leg stretched during all respiration cycles to identify the best approach and to avoid artifacts caused by the thorax. For a diagnosis of hepatic steatosis, the following features were recorded: (1) ultrasonographic contrast between the liver and right kidney parenchyma; (2) brightness of the liver; (3) deep attenuation of ultrasound penetration into the deep portion of the liver and impaired visualization of the diaphragm; and (4) impaired visualization of the borders of intrahepatic vessels and narrowing of their lumen. Trained technicians perform ultrasonography with a 5 mega-Hertz transducer (Ch5-2, Siemens, Mountain View, CA). The overall gain, initial gain, and time gain compensation settings were kept within a narrow range. The ultrasonographic images were read and interpreted by a single blinded expert reader.

Carotid ultrasound to evaluate subclinical atherosclerosis was performed with the Siemens Acuson X300 ultrasound system (Malvern, PA) using a VF 13-5 linear array transducer as described in previous studies.[14] The protocol was designed following guidelines from the American Society of Echocardiography consensus statement on subclinical vascular disease.[20] Both left and right common carotid arteries were imaged from 3 different angles for a total of 6 images: anterior, lateral, and posterior images for both common carotid arteries.

Carotid plaque presence was determined by examining the carotid bulb, its bifurcation and the carotid branch arteries in addition to the common carotid artery. Carotid IMT was measured using the Carotid Analyzer software (Medical Imaging Applications, Coralville, IA), a semi-automated border detection program. Measurements were made at the R-wave of the electrocardiogram on a minimum of 2 clips from each side and the results were averaged. Mean cIMT was categorized as being either < or ≥75th percentile for age and gender.[20] Carotid plaque was defined as an area of wall thickening that was >50% of the thickness of the surrounding wall. A single blinded expert reader similarly performed all measurements. Replicate readings were performed on 5% of the cohort and the intra-class correlation coefficient for our laboratory was 0.96. Abnormal carotid ultrasound study was defined as mean cIMT thickness ≥75th percentile for age and gender and/or the presence of carotid plaque.

All descriptive results and the models reported were adjusted for the probability of sampling using age and gender adjusted sampling weights and taking into consideration clustering effects arising from multiple participants from the same household as well as census tracks and blocks.[13] Descriptive statistics of baseline demographics and clinical characteristics were reported and compared by NAFLD/Abnormal Carotid Ultrasound groups. Data were summarized as mean and standard error for continuous variables and frequency and weighted column percentages for categorical variables. Continuous variables were compared using survey-weighted linear regression models from which Tukey-Kramer-adjusted p values were calculated. Survey-weighted logistic regression was used to compare categorical variables and to obtain the Rao-Scott F-adjusted chi-square p values. Survey-weighted multivariable linear regression model was constructed to evaluate the effect of abnormal fatty liver ultrasound on cIMT adjusting for demographic and clinical variables found to be significantly associated with cIMT with p-value<0.05. To determine factors associated with both abnormal liver and abnormal carotid, we conducted survey-weighted multinomial multivariable logistic regression. Potential multi-collinearity and interaction effects across the predictors in the multivariable models were assessed. All analyses were performed using SAS 9.3 (SAS, 2000). Statistical significance was set at $p < 0.05$.

## RESULTS

Demographic and biochemical characteristics are listed in Table 1. This study included 407 individuals with an average age of 50.4 ± 1.2 years and females making up 58.3% of the sample. There was a high prevalence of coronary risk factors in this cohort. The majority of the individuals were either overweight or obese (85.6%), and only 14.4% had a normal body mass index (BMI) [mean BMI of 31.0 ± 0.4 kg/m$^2$].

NAFLD was demonstrated in nearly half (49.2%) of the study participants with no gender difference in prevalence (42.2% in males and 57.8% in females, p=0.8800). Compared to subjects without NAFLD, subjects with NAFLD had higher BMI (32.5±0.5 kg/m$^2$ versus 29.5±0.7 kg/m$^2$; p=0.0005), larger waist circumference (106.5±1.2 centimeter. versus 100.2±1.6 centimeter; p=0.0024), had higher fasting blood glucose (114.9±5.3 milligram/deciliter versus 99.8±1.6 milligram/deciliter; p=0.0058) and hemoglobin A1C (6.4%±0.2 versus 5.8%±0.1; p=0.0006), had higher fasting triglycerides (168.6±7.6 milligram/deciliter

versus 127.0±6.4 milligram/deciliter; p<0.0001), had higher Homeostasis Model Assessment Insulin Resistance Index (4.7±0.6 versus 3.1±0.3, p=0.0225), had lower high density lipoprotein cholesterol levels (43.0±1.1 milligram/deciliter versus 47.8±1.6 milligram/deciliter; p=0.0107), and lower adiponectin levels (14.6±1.3 micrograms versus 20.8±1.4 micrograms; p=0.0017). Patients with NAFLD had higher prevalence of metabolic syndrome compared to those without (70.1% versus 38.5%; p<0.0001). Age, gender, family history, blood pressure, low-density lipoprotein cholesterol, level of physical activity, high-sensitivity C-reactive protein, and other inflammatory markers did not differ significantly between the two groups.

The mean cIMT for the cohort was 0.7 ± 0.0 millimeter, with no gender differences (p=0.4966). There was no difference in mean cIMT between those with NAFLD vs. those without NAFLD (p=0.2679). More than one third of the cohort (35.1%) had abnormal carotid ultrasound findings. Among those with NAFLD, 30.4% had evidence of subclinical atherosclerosis. When participants were categorized into four groups based on normal or abnormal carotid and liver ultrasound studies (Table 1 and Figure 1), there was a graded increase in prevalence for metabolic syndrome (p<0.0001), obesity (p<0.0001), and diabetes mellitus (p<0.0001) among groups.

Using a multivariable survey weighted logistic regression model, the odds of the presence of both abnormal carotid and liver ultrasound vs. normal carotid and liver ultrasound increased by 5% with each 1 milligram/deciliter increase in fasting plasma glucose (odds ratio=1.05, 95% confidence interval 1.02–1.08), after controlling for age, gender, family history, BMI, systolic blood pressure, fasting triglycerides, physical activity, and smoking status. In further analysis, after controlling for covariates, using multivariable survey weighted linear regression models in age domains, NAFLD was independently associated with mean cIMT in younger individuals of ages < 45 years (p=0.0309), but not in older individuals of ages ≥ 45 years (p=0.1891).

## DISCUSSION

This study shows for the first time that in young Mexican Americans (< 45 years of age), the presence of NAFLD portends an increased risk of subclinical atherosclerosis independent of traditional coronary risk factors. Although the independent association between NAFLD and subclinical atherosclerosis has been demonstrated in young individuals by other investigators,[21–22] these studies involved non-Hispanic Whites and Blacks. To our knowledge, this study is the first demonstration of this phenomenon in Hispanics. With a national prevalence of approximately 20%, NAFLD is becoming a public health concern with rising diabetes and obesity rates yearly especially in younger individuals. Indeed, in our cohort, NAFLD was seen in nearly half of the sample (49.2%), which is more than twice the prevalence reported nationally. Our study highlights the importance of screening for subclinical atherosclerosis in individuals with NAFLD especially in those persons < 45 years of age. The presence of NAFLD should alert the clinician to screen for early atherosclerosis, with the goal of intensification of risk factor modification to reduce the risk of a first cardiovascular disease event.

We, along with others, have demonstrated very high prevalence of cardiovascular risk factors among Hispanics,[9,14,23] with Mexican Americans showing epidemic proportions for obesity, diabetes, and the metabolic syndrome.[14] The high prevalence of NAFLD in this minority group is therefore not surprising, and our present study is consistent with previous reports that showed that individuals with NAFLD were more likely to be obese, diabetic, dyslipidemic, and have increased visceral adiposity. In this study, we also demonstrated that, among Mexican Americans, adiponectin levels were lower in those with NAFLD compared to those without NAFLD. This finding has also been found amongst Asians and non-Hispanic Whites[24–25] but to our knowledge is the first time to be reported among Mexican Americans. Hypoadiponectinemia is hypothesized to be part of a general metabolic disturbance characterized by ectopic fat accumulation in the central compartment and dysfunctional adipose tissue.[25] Our finding of reduced adiponectin levels in Mexican Americans with NAFLD is consistent with these findings and supports the role of adipocytokines in metabolism and glucose tolerance.

Impaired fasting glucose is a major component of the metabolic syndrome. In this study, among the cardiometabolic risk factors evaluated, only fasting plasma glucose remained an independent risk factor for both NAFLD and subclinical atherosclerosis, after adjusting for covariates in this cohort. For every 1 milligram/deciliter increase in fasting plasma glucose, there was an increase in the odds of having both NAFLD and subclinical atherosclerosis by 5%. This is another novel finding, and is particularly relevant among Hispanics who have a very high prevalence of diabetes and prediabetes. In this study, the association between fasting plasma glucose and both NAFLD and subclinical atherosclerosis was independent of BMI, waist circumference, or physical activity, suggesting that these factors do not modify the risk for having both conditions. On the other hand, fasting plasma glucose appears to be an important determinant for increased risk of both hepatic and vascular end organ damage in this cohort. This is an intriguing finding, as it seems to emphasize the importance of glucose control among diabetics and plasma glucose level maintenance in those who are not, thereby posing potential therapeutic targets for prevention of these diseases in Mexican Americans.

A few limitations must be noted. This was a cross-sectional study and as such no causal relationships can be made, however longitudinal follow-up studies are currently underway. Although liver biopsy and magnetic resonance spectroscopy are considered the gold standards for the diagnosis of NAFLD,[26] these are invasive and/or expensive tests, which are not feasible in this community dwelling cohort. Since individuals found to have NAFLD by ultrasonography had to be at least in the moderate stage of the disease and this technique can miss mild cases, the findings in this study represent probably more advanced disease states thus increasing specificity of the diagnosis. In this study, we did not perform imaging studies to quantitate visceral adiposity and more sensitive measures of central adiposity may yield different results; these studies are underway.

## Acknowledgments

This work was supported by MD000170 P20 funded from the National Center on Minority Health and Health Disparities, and the Centers for Translational Science Award 1U54RR023417-01 from the National Center for Research Resources.

We would like to acknowledge Dr. Belinda Reininger for her help with the physical activity data. We thank our cohort team, particularly, Rocio Uribe, Emma Molina, Jody Rodriguez, and their team, who not only recruited and documented the participants, but also performed the ultrasound studies under expert supervision. We also thank Marcela Montemayor and Israel Hernandez and their teams for laboratory and data support, and Norma Perez-Olazaran and Christina Villarreal for administrative support. We thank Valley Baptist Medical Center, Brownsville, Texas for providing us space for our Center for Clinical and Translational Science Clinical Research Unit. We also thank the community of Brownsville and the participants who so willingly participated in this study in their city.

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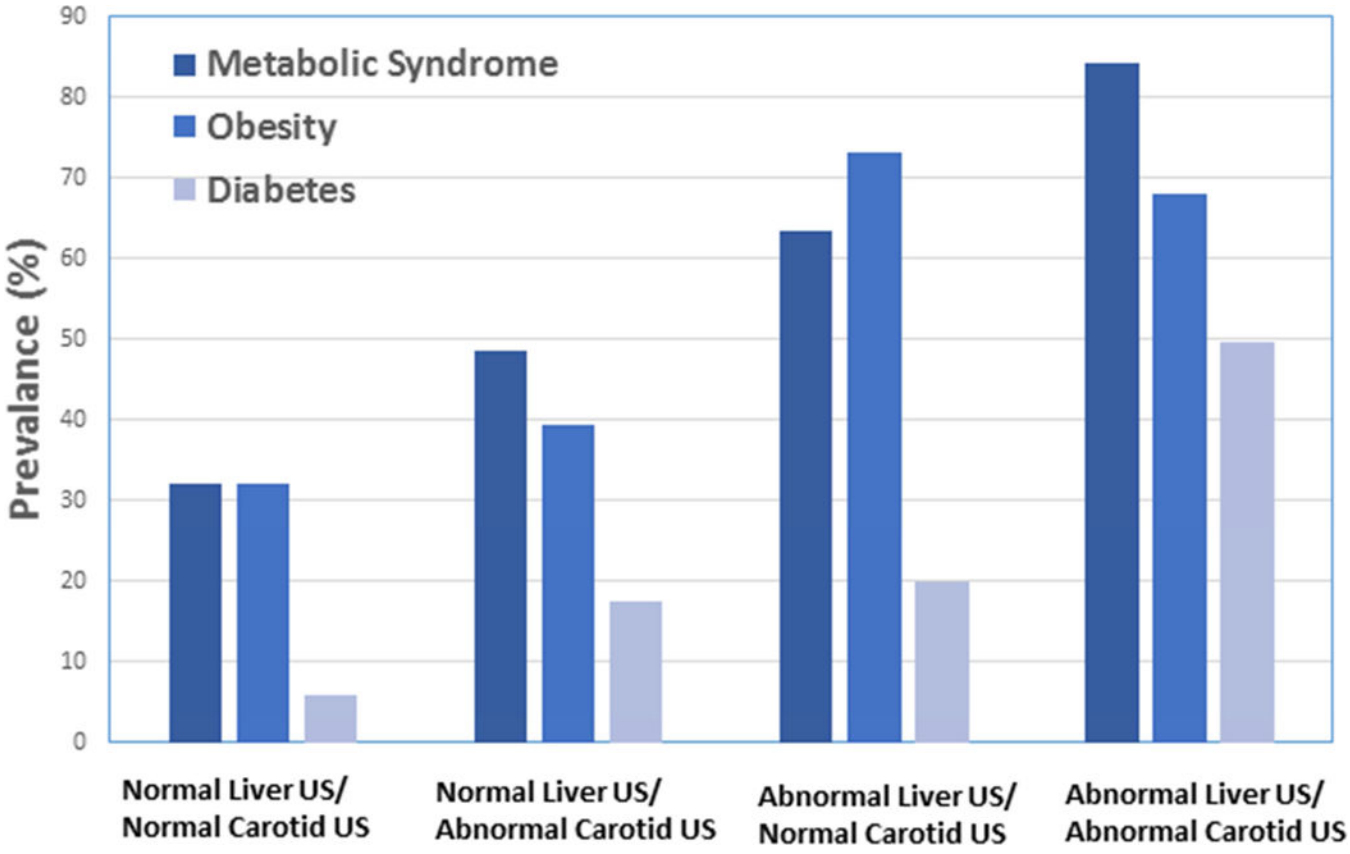


**Figure 1.**

Weighted Prevalence of Metabolic Syndrome, Obesity and Diabetes among Mexican Americans within Non-Alcoholic Fatty Liver Disease/Subclinical Atherosclerosis Groups. (NAFLD = Non-Alcoholic Fatty Liver Disease)

**Table 1**

Cohort Demographics and Metabolic Characteristics. *Student's t-test for continuous variables and Chi-square test for categorical variables.

| | | Normal Liver | | Presence of NAFLD | | |
|---|---|---|---|---|---|---|
| | Total Cohort | Normal Carotid Study | Abnormal Carotid Study | Normal Carotid Study | Abnormal Carotid Study | |
| | n=407 | n=129 | n=70 | n=148 | n=60 | p-value |
| **Continuous Variable, mean ± SEM** | | | | | | |
| Age (years) | 50.4±1.2 | 44.7±1.7 | 60.8±2.2 | 48.1±1.4 | 53.4±2.5 | **<0.0001** |
| Body Mass Index (kg/m$^2$) | 31.0±0.4 | 29.8±0.9 | 29.1±0.9 | 32.5±0.4 | 32.6±1.4 | **0.0018** |
| Waist Circumference (cm) | 103.3±1.0 | 99.6±2.4 | 101.2±2.1 | 105.5±1.2 | 108.8±2.2 | **0.0141** |
| Systolic Blood Pressure (mm Hg) | 120.9±1.2 | 115.3±1.5 | 126.7±2.6 | 120.8±1.8 | 124.9±3.6 | **0.0005** |
| Diastolic Blood Pressure (mm Hg) | 73.9±0.6 | 72.1±0.8 | 73.0±1.7 | 75.4±1.0 | 75.4±1.5 | **0.0421** |
| Fasting Blood Glucose (mg/dL) | 107.2±2.9 | 95.2±1.2 | 106.8±3.3 | 104.9±2.9 | 137.7±15.4 | **<0.0001** |
| Total Cholesterol (mg/dL) | 182.7±2.4 | 176.7±3.9 | 182.2±6.4 | 183.6±3.7 | 193.6±7.1 | 0.1692 |
| Triglycerides (mg/dL) | 147.4±5.2 | 124.9±9.1 | 130.2±8.9 | 160.5±9.3 | 186.9±13.3 | **0.0002** |
| High Density Lipoprotein (mg/dL) | 45.5±1.0 | 46.6±1.2 | 49.8±3.5 | 43.0±1.2 | 43.3±2.1 | 0.0641 |
| Low Density Lipoprotein (mg/dL) | 107.7±2.0 | 105.4±3.8 | 105.6±5.4 | 108.4±3.2 | 113.8±5.7 | 0.6154 |
| High Sensitivity C-Reactive Protein <10 (mg/L)[1] | 3.2±0.3 | 3.6±0.6 | 2.7±0.5 | 3.2±0.5 | 3.7±0.8 | 0.6029 |
| Adiponectin (mcg/mL) | 18.1±1.1 | 19.8±1.5 | 22.0±2.6 | 15.0±1.5 | 13.8±1.6 | **0.0109** |
| Homeostasis Model Assessment Insulin Resistance Index | 3.9±0.3 | 2.9±0.3 | 3.4±0.6 | 3.8±0.3 | 6.6±1.6 | **0.0445** |
| Hemoglobin A1C, % | 6.1±0.1 | 5.6±0.1 | 6.1±0.1 | 6.0±0.1 | 7.0±0.4 | **<0.0001** |
| Mean Carotid Intima Media Thickness (mm) | 0.7±0.0 | 0.6±0.0 | 0.8±0.0 | 0.6±0.0 | 0.8±0.0 | **<0.0001** |
| Annual Household Income ($) | $36,547±$3,632 | $38,252±$6,630 | $40,308±$7,932 | $30,321±$4,183 | $42,322±$9,108 | 0.3692 |
| Education Amount (years) | 10.5±0.3 | 10.5±0.5 | 10.6±0.8 | 10.5±0.5 | 10.3±0.9 | 0.9925 |
| Total MET-minutes of moderate and vigorous activity per week | 834.8±175.6 | 1288.4±466.2 | 844.7±297.7 | 672.5±215.0 | 196.9±87.8 | **0.0152** |
| **Categorical Variable Weighted Frequency** | | | | | | |
| Female | 273 (58.3%) | 89 (63.7%) | 44 (51.5%) | 92 (63.4%) | 50 (85.1%) | 0.4147 |
| Smoker | 108 (29.1%) | 25 (18.9%) | 25 (50.3%) | 38 (26.4%) | 20 (30.5%) | **0.0070** |
| Metabolic Syndrome | 223 (54.0%) | 43 (32.0%) | 39 (48.6%) | 91 (64.4%) | 50 (85.0%) | **<0.0001** |

| | | Normal Liver | | Presence of NAFLD | | |
|---|---|---|---|---|---|---|
| | **Total Cohort** | **Normal Carotid Study** | **Abnormal Carotid Study** | **Normal Carotid Study** | **Abnormal Carotid Study** | |
| | **n=407** | **n=129** | **n=70** | **n=148** | **n=60** | **p-value** |
| Central Obesity[2] | 389 (96.1%) | 120 (94.2%) | 67 (96.1%) | 142 (96.1%) | 60 (100.0%) | 0.7837 |
| Obesity | 214 (52.4%) | 43 (32.1%) | 29 (38.6%) | 101 (71.8%) | 41 (68.6%) | **<0.0001** |
| Hypertension[3] | 171 (43.3%) | 39 (29.6%) | 37 (54.3%) | 55 (37.9%) | 40 (68.7%) | **0.0003** |
| Family history of stroke or heart attack | 50 (13.0%) | 13 (6.7%) | 12 (15.3%) | 17 (17.0%) | 8 (13.6%) | 0.2123 |
| Total Cholesterol ≥200 mg/dL | 120 (29.5%) | 31 (25.3%) | 27 (30.6%) | 32 (23.8%) | 30 (42.3%) | **0.0477** |
| Triglycerides ≥ 150 mg/dL | 151 (36.6%) | 35 (26.5%) | 22 (21.3%) | 64 (46.6%) | 30 (55.5%) | **0.0005** |
| High Density Lipoprotein <40 mg mg/dL in Males and <50 mg/dL in Females | 233 (54.7%) | 65 (50.4%) | 30 (36.5%) | 99 (63.5%) | 39 (68.1%) | **0.0127** |
| Low Density Lipoprotein ≥ 130 mg/dL | 89 (23.6%) | 26 (23.1%) | 18 (29.9%) | 24 (18.3%) | 21 (28.1%) | 0.5305 |
| Diabetes Mellitus[4] | 95 (20.9%) | 10 (6.4%) | 20 (18.4%) | 35 (21.6%) | 30 (50.5%) | **<0.0001** |
| High Sensitivity C-Reactive Protein >3.0 mg/dL[1] | 52 (45.5%) | 16 (47.9%) | 9 (38.2%) | 20 (48.0%) | 7 (51.1%) | 0.8953 |
| Met minimum recommendations for physical activity of ≥ 600 MET-minutes/week | 94 (28.5%) | 42 (38.3%) | 12 (27.6%) | 32 (27.4%) | 8 (10.8%) | **0.0406** |

Data are adjusted for the probability of sampling using weights taking into consideration clustering effects arising from the same census block and household.

[1]High Sensitivity C-Reactive Protein ≥10 mg/L excluded

[2]Central Obesity defined as waist circumference ≥102 cm in males and ≥88 cm in females

[3]Hypertension defined as blood pressure ≥130 mm Hg systolic and/or 85 mm Hg diastolic or the regular use of anti-hypertensive medication

[4]Diabetes Mellitus defined based on 2010 American Diabetes Association definition (Hemoglobin A1C ≥6.5%, fasting plasma glucose ≥126 mg/dL, two-hour plasma glucose ≥200 mg/dL during 75 gram oral glucose tolerance test, or random plasma glucose ≥200 mg/dL associated with classic symptoms of hyperglycemia or hyperglycemic crises)