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## Association between Non-Alcoholic Liver Disease and Chronic Kidney Disease: An Ultrasound Analysis from NHANES 1988–1994

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### Abstract

**Background/ Aims**—Non-alcoholic fatty liver disease (NAFLD) has been proposed to contribute to chronic kidney disease (CKD) independently of traditional cardiometabolic risk factors. We hypothesized that NAFLD is associated with CKD and that greater severity of NAFLD is associated with higher odds of CKD.

**Methods**—A cross-sectional analysis of 11,469 adults who participated in the National Health and Nutrition Examination Survey 1988–1994. NAFLD was defined by ultrasonographic detection of steatosis in the absence of other liver diseases. CKD was defined as an estimated glomerular filtration rate of  $\leq 60$  mL/min/1.73 m<sup>2</sup> or the presence of albuminuria in subjects with an estimated glomerular filtration rate of  $>60$  mL/min/1.73 m<sup>2</sup>.

**Results**—2,891 (25.4%) patients in the cohort had CKD. The prevalence of NAFLD was higher in individuals with CKD compared to those without CKD (42.2% vs. 34.5%,  $p<0.0001$ ). NAFLD was associated with CKD in unadjusted logistic regression analysis (odds ratio 1.47, 95% confidence interval 1.29–1.67,  $p<0.0001$ ). Adjustment for demographics and components of metabolic syndrome attenuated this relationship (odds ratio 1.04, 95% confidence interval 0.88–1.23,  $p=0.64$ ). Moderate and severe NAFLD on ultrasound were increasingly associated with prevalent CKD in unadjusted analysis but not after adjustment for metabolic syndrome components.

**Conclusion**—After adjusting for features of metabolic syndrome, ultrasound-diagnosed NAFLD is not associated with prevalent CKD among US adults. Aggressive public health efforts are needed to prevent and treat metabolic syndrome.

### Keywords

chronic kidney disease; nonalcoholic fatty liver disease; NHANES

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) has become increasingly common over the past few decades, with prevalence estimates at 20–30% in the United States (US), Europe and

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Asia.[1–2] Now the most common chronic liver disease in the developed world, its increase in prevalence may be related to its pathogenetic association with the burgeoning epidemics of obesity and metabolic syndrome.[3] This etiologic background has resulted in increasingly recognized associations between NAFLD and other conditions that are pathogenically related to metabolic syndrome, such as cardiovascular disease.[4–5]

Similarly, Chronic kidney disease (CKD), is strongly associated with metabolic syndrome and cardiovascular disease.[6–8] In addition to shared risk factors with cardiovascular and kidney disease, it has been proposed that NAFLD itself may contribute to subclinical systemic inflammation and endothelial dysfunction, [9–10] as such contributing to kidney and cardiovascular disease. Consistent with this hypothesis, a few observational studies have shown an association of NAFLD with prevalent CKD independently of traditional cardiometabolic risk factors. [11–14]

Liver ultrasound, a non-invasive and widely available diagnostic tool, has emerged as a viable alternative to liver biopsy in large, population-based studies of NAFLD. The role of ultrasound in the diagnosis of NAFLD has been enhanced by the development of a radiographic scoring system that has ameliorated previous concerns regarding intra- and inter-observer reliability.[15] Liver ultrasound data is newly available from the National Health and Nutrition Examination Survey III (NHANES 1988–1994). In this study, we hypothesized that NAFLD is associated with prevalent CKD, independently of cardiometabolic risk factors and that greater severity of NAFLD by ultrasound is associated with higher odds of CKD.

## SUBJECTS AND METHODS

### Study population

Our analysis is based upon data from the NHANES program, a 40 year-old research initiative run by the National Center for Health Statistics. Cross-sectional demographic, socioeconomic, dietary, and medical data were collected through surveys, physical examination, and laboratory testing, with over-sampling of African Americans, Hispanics, and those over 60 years of age in order to obtain a representative sample of the US adult population.

The database contained 14,797 participants aged 20–74 years who had undergone liver ultrasonography. Individuals with ungradable or inadequate imaging, individuals with viral hepatitis B or C, those who reported excessive alcohol intake ( $\geq 2$  drinks/day), and those with incomplete laboratory or clinical data were excluded from analysis. As a result, 11,469 subjects met our criteria and were included in final analysis. (Figure 1)

### Predictors and outcome measure

The independent variable was the presence of NAFLD, as detected by ultrasound. As part of the NHANES program, ultrasonography had been performed through longitudinal and transverse scanning of the right upper quadrant with the patient in both the supine and left lateral decubitus positions. In 2009–2010, trained ultrasound readers examined video recordings of these ultrasounds, specifically evaluating the liver imaging for evidence of hepatic steatosis based on standardized criteria.

Briefly, criteria for the diagnosis and characterization of NAFLD include hepatorenal echo contrast, liver parenchymal brightness, deep beam attenuation, and vessel blurring.[15] Hepatorenal echo contrast and liver brightness were considered together and assigned a combined score on a 0–3 scale. Deep attenuation was scored from 0–2, and vessel blurring) was scored 0–1. These three separate scores were totaled and, using an algorithm,

transformed into an overall NAFLD score that ranged from 1–4, in which 1 = absent, 2 = mild, 3 = moderate, and 4 = severe.[16]

The dependent variable of interest was the presence of CKD, defined as either an estimated glomerular filtration rate (eGFR) of  $\leq 60$  mL/min/1.73 m<sup>2</sup> or the presence of albuminuria. eGFR calculation was based on the abbreviated Modification of Diet in Renal Disease (MDRD) study formula:  $eGFR = 186.3 \times (\text{serum creatinine in mg/dl})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ if female}) \times (1.21 \text{ if black})$ . Albuminuria was defined as a spot urinary albumin-to-creatinine ratio that exceeded 30 mg/g.

### Other covariates

Covariates were chosen based on prior studies and their biological plausibility. The following covariates were included in the logistic regression analysis: age, sex, race, history of hypertension, history of diabetes, systolic blood pressure (BP), waist circumference, triglycerides, high density lipoprotein (HDL) cholesterol, and the homeostasis model assessment of insulin resistance (HOMA-IR).

History of hypertension was defined as a physician diagnosis of hypertension or the use of anti-hypertensive medications. History of diabetes was defined as a physician diagnosis of diabetes or the use of diabetic medications. Systolic BP was measured by physicians at mobile examination centers with mercury sphygmomanometers using a standard protocol. Waist circumference was measured according to NHANES manual of procedures, in which tape is applied above the upper border of the right ilium horizontally and then tightened slightly to measure the waist circumference in centimeters (to the nearest millimeter).[16] Fasting levels of triglycerides and HDL cholesterol were measured enzymatically with a Hitachi 704 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). HOMA-IR score was calculated using the HOMA-IR formula ( $\text{HOMA-IR} = \text{fasting insulin (mU/l)} \times \text{fasting glucose (mmol/l)} / 22.5$ ; the fasting glucose used in this equation was measured by the hexokinase method, and fasting insulin was measured using the Merocodia Insulin ELISA).

### Statistical analysis

Due to the complex sample strategy of NHANES 1988–1994, appropriate 6-year weights and strata were applied. SAS (9.2) PROC SURVEYMEANS and SURVEYFREQ were used to obtain descriptive statistics for the population. Analysis was performed using the Rao-Scott Chi squared test for categorical variables and oneway ANOVA for continuous variables. Logistic regression analysis was applied to examine whether the presence of NAFLD was associated with prevalent CKD. Results are expressed as odds ratios (OR) with 95% confidence intervals (95% CI). Three separate logistic regression models were applied: an unadjusted model; a model adjusted for age, sex and race (Model 1); and a model adjusted for history of hypertension, history of diabetes, systolic BP, waist circumference, triglycerides, HDL-cholesterol and HOMA-IR score (Model 2). Logistic regression modeling was also done to examine any association between CKD and the ultrasonographic severity of NAFLD (mild, moderate and severe). Because diabetes is a well-established and independent risk factor for both NAFLD and CKD, we stratified by diabetes status. Since only 62% of all participants fasted appropriately prior to measurement of triglycerides and insulin levels, we conducted a sensitivity analysis excluding triglycerides and HOMA-IR from the model and then excluding non-fasting individuals from the full multivariate model (Model 2). All statistical analyses were performed using SAS 9.2 software.

## RESULTS

### Clinical characteristics of participants

Of the 11,469 participants, 2,891 (25.4%) had CKD and 8,578 (74.5%) did not. Clinical characteristics of the study participants stratified by CKD status are shown in Table 1. Compared to individuals without CKD, those with CKD were older, were more likely to be female and white, and had higher values of waist circumference, systolic BP, plasma triglycerides and HOMA-IR score, and lower HDL-cholesterol levels. Subjects with CKD were also far more likely to have a history of hypertension and diabetes than those without CKD.

### Relationship between ultrasound-diagnosed NAFLD and prevalent CKD

A higher percentage of patients with CKD were found to have NAFLD on ultrasound when compared to those without CKD (42.2% vs. 34.5%;  $p < 0.0001$ ). As shown in Table 1, this increased overall prevalence was mainly due to the higher prevalence of moderate and severe NAFLD in the CKD population, as both groups had similar rates of mild NAFLD on ultrasound (13.3% vs. 13.6% in the CKD and non-CKD groups, respectively).

As shown in Table 2, logistic regression analysis using an unadjusted model determined that the OR for the presence of CKD amongst patients with NAFLD was 1.47 (95% CI 1.29–1.67,  $p < 0.0001$ ) when compared to patients without NAFLD. After adjusting for age, sex, and race (Model 1), subjects with NAFLD remained at increased odds of prevalent CKD (OR 1.21, 95% CI 1.04–1.40,  $p = 0.014$ ). Further adjustment for cardiometabolic risk factors (Model 2) attenuated this relationship (OR 1.04, 95% CI 0.88–1.23,  $p = 0.64$ ).

### Relationship between NAFLD severity and prevalent CKD

Individuals with severe NAFLD by ultrasound were found to have an unadjusted OR for prevalent CKD of 1.96 (95% CI 1.53–2.51,  $p < 0.001$ ) when compared to patients without NAFLD. Adjustment for age, race and sex (Model 1) yielded an OR of 1.44 (95% CI 1.05–1.96,  $p = 0.02$ ). However, after adjusting for the cardiometabolic risk factors in Model 2, the OR of CKD was 1.17 (95% CI 0.83–1.65,  $p = 0.38$ ). Similar to severe NAFLD, moderate NAFLD by ultrasound was associated with higher odds of CKD in unadjusted analysis (OR 1.64, 95% CI 1.38–1.94,  $p < 0.0001$ ). This relation remained significant after adjusting for demographics (OR 1.24, 95% CI 1.03–1.50,  $p = 0.03$ ), but was no longer significant after additional adjustment for cardio-metabolic risk factors (OR 1.01, 95% CI 0.82–1.24,  $p = 0.92$ ). There was no association between mild NAFLD by ultrasound and CKD in unadjusted or adjusted logistic regression analysis (Figure 2).

### Association between NAFLD and CKD by diabetes status

There was no association between NAFLD and CKD in individuals with diabetes neither in unadjusted nor in adjusted regression analyses. Conversely, in subjects without diabetes, the OR for CKD in NAFLD was 1.40 (95% CI 1.22–1.61,  $p < 0.0001$ ) in unadjusted analysis, and 1.20 (95% CI 1.03–1.41,  $p = 0.022$ ) after adjusting for demographics. The association between NAFLD and CKD was attenuated, however, after further adjustment for the covariates included in Model 2 (Table 3).

Of note, the association between NAFLD and CKD remains not significant in the whole population and in the participants with and without diabetes mellitus if triglycerides and HOMA-IR are removed from model 2. Similarly, if the non-fasting individuals are excluded from the analysis, there is no significant association between NAFLD and CKD in the fully adjusted model.

## DISCUSSION

This analysis represents the first inquiry into whether an association between ultrasound-diagnosed NAFLD and CKD exists in a large, nationally representative sample of the US population. Our data demonstrate a significant, positive association between NAFLD and prevalent CKD in univariate analysis. This relationship persisted after adjustment for demographics but was attenuated by adjusting for features of metabolic syndrome. In addition, we report that increasing severity of NAFLD on ultrasound was significantly associated with a greater age, sex and race-adjusted prevalence of CKD. The association between the ultrasonographic severity NAFLD and prevalent CKD was also attenuated after adjustment for features of metabolic syndrome.

It has been proposed that NAFLD itself, independently of obesity and other metabolic disorders, could contribute to the development and progression of CKD. In the setting of visceral obesity, insulin resistance leads to increased peripheral lipolysis and a consequent influx of free fatty acids into the liver.[10] The concurrent chronic hyperinsulinemia induces intra-hepatic triglyceride production,[17] and the consequently increased triglyceride content in the liver (i.e., pure steatosis) can progress to NASH in the presence of oxidative stress and inflammation.[18–20] These hepatic necroinflammatory changes may exacerbate systemic/hepatic insulin resistance and the metabolic syndrome, and have been suggested to contribute to the development and progression of CKD.

In addition, NAFLD, especially in its necro-inflammatory form, may release a variety of cytokines and pro-inflammatory mediators (such as leptin, resistin, interleukin- 6, tumor necrosis factor- $\alpha$  and transforming growth factor-beta)[21] that may play a role in CKD pathogenesis.[22] Additionally, decreased levels of adiponectin seen in NAFLD may produce pathological changes in the kidney.[23] The possibility of these pathways producing a link between NAFLD and CKD independent of metabolic syndrome components has been also supported by some recent prospective studies that have shown that pre-existing NAFLD can predict new onset CKD in individuals with[14] and without diabetes.[11]

While the cross-sectional nature of our study precludes us from drawing conclusions about causality between the two disorders in question, the fact that controlling for the features of metabolic syndrome attenuated the association between NAFLD and CKD suggests that the relationship between both diseases may be confounded by some common pathophysiological mechanisms and shared cardiometabolic risk factors. This is contrary to the findings of other studies where NAFLD (diagnosed by ultrasound) was associated with incident CKD in a community-based cohort of apparently healthy Korean men[11] independently of obesity, hypertension, and other features of metabolic syndrome. Of note, we found no gender differences in NAFLD's relationship to CKD (data not shown).

We found no association between NAFLD and CKD in individuals with diabetes in unadjusted or adjusted regression analyses, which contrasts with previous reports of an independent association between these two diseases in people with diabetes.[14, 24] This difference may result from a smaller sample size of diabetic individuals in this study compared to prior studies in type 2 diabetics.[13] It is also possible that other factors such as ethnic composition, age, duration of diabetes, and dietary habits of our population may have played a role in our findings.

In addition to the cross-sectional nature of this analysis, our study has several limitations. Ultrasound is relatively insensitive to the presence of smaller amounts of hepatic steatosis, cannot distinguish NASH from other forms of NAFLD, and suffers from problems with inter-observer variability, [25] although its noninvasive nature makes it ideal for such large

epidemiological studies. In addition, while a large proportion of CKD stems from disease processes associated with metabolic syndrome, some CKD is pathogenically independent of this background (e.g., glomerulonephritis or polycystic kidney disease), and this study did not distinguish between the various causes of renal impairment.

Despite these limitations, this analysis has several important strengths. First, it is the largest and most comprehensive survey to examine the association between ultrasound-diagnosed NAFLD and the presence of CKD in a nationally representative sample of US adults. Second, NHANES-III used a standardized scoring system to screen for NAFLD with ultrasound and characterize its severity. Third, the availability of extensive and complete data on a wide range of cardio-renal risk factors allowed us to provide an unbiased estimate of the relationship between NAFLD and CKD. Finally, the design of NHANES-III allows the results to be extrapolated to the entire US civilian, non-institutionalized, adult population.

In conclusion, our findings demonstrate a significant, positive association between the presence and severity of ultrasonographic NAFLD and CKD in US adults in unadjusted analysis. However, this association was attenuated by adjusting for features of metabolic syndrome, thus supporting the hypothesis that these two diseases may be linked as a result of the shared cardiometabolic risk factors. As such, it is of great importance to implore public health efforts and strategies to curb the epidemics of obesity and metabolic syndrome. Otherwise, the prevalence of NAFLD and CKD will continue to rise.

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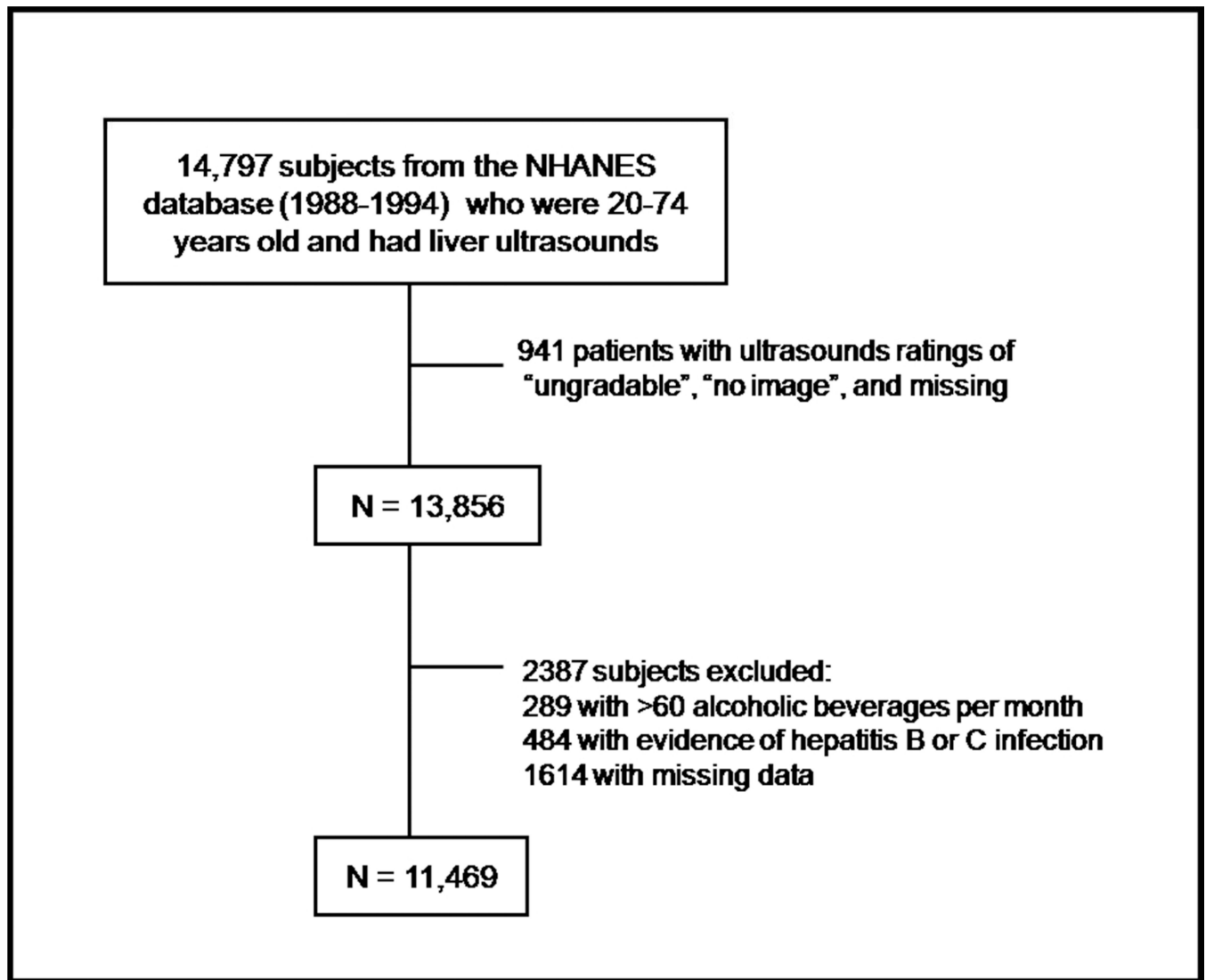
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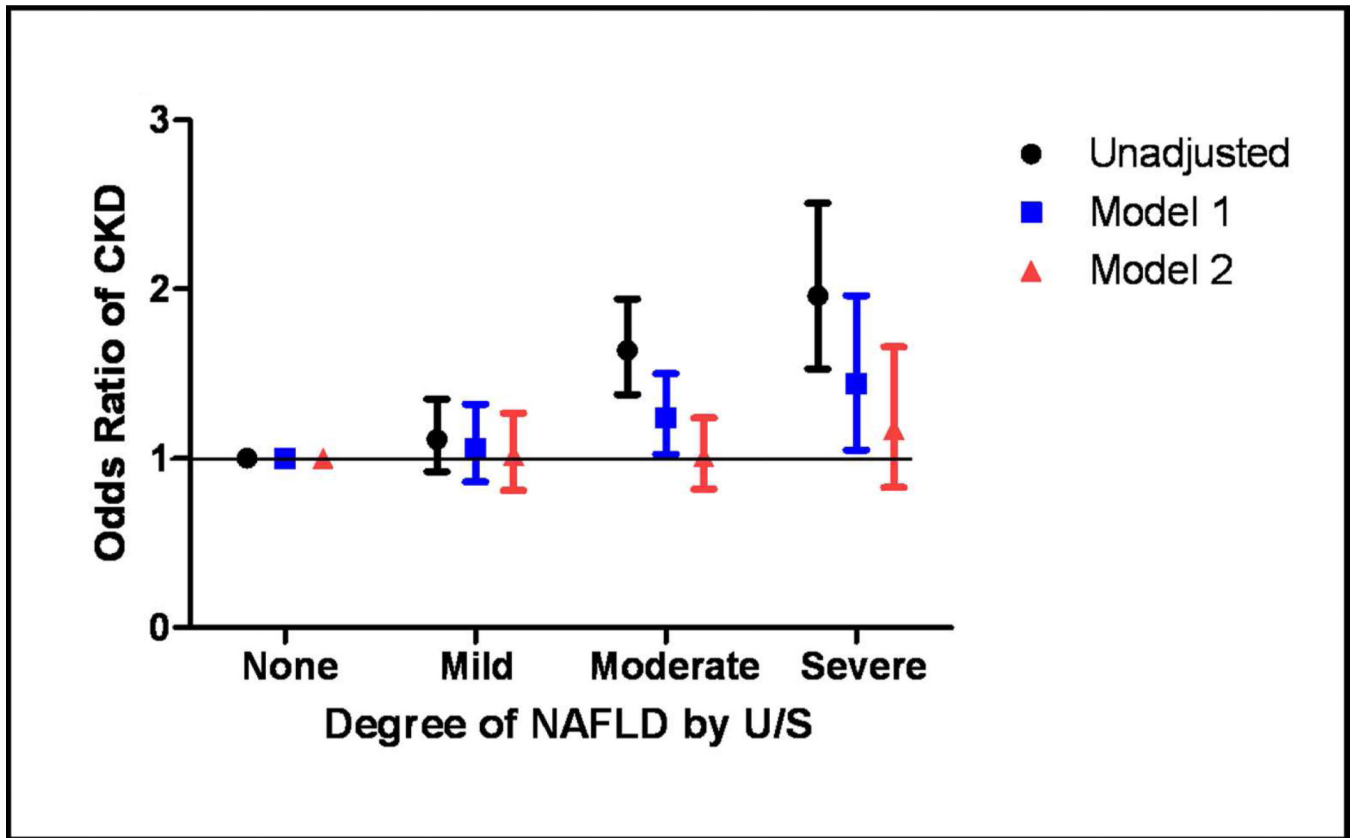
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**Figure 1. Study population**

Of the initial 14,797 eligible candidates for the study, a total of 11,469 subjects met inclusion and exclusion criteria and were included in analysis.





**Figure 2. Odds of prevalent CKD in patients with different ultrasonographic severity of NAFLD as compared to patients without NAFLD**

In unadjusted analysis, moderate and severe NAFLD were associated with a statistically significant increase in the odds ratio for CKD. This remained significant after adjusting for age, sex and race, but was attenuated after further adjustment for metabolic syndrome components.

**Table 1**

Demographic and clinical characteristics of the study population, grouped by CKD status

Characteristic	no CKD (n = 8578)	CKD (n = 2891)	p-value
Age (years)	38 ± 0.20	53 ± 0.38	< 0.0001
Sex (% male)	48.0	37.1	< 0.0001
Race			
% White	64.7	75.4	< 0.0001
% Black	31.4	21.6	
% Mexican-American	0.05	0.03	
% other	3.9	3.0	
History of hypertension (%)	19.1	41.8	< 0.0001
History of diabetes (%)	4.8	15.2	< 0.0001
Systolic BP (mmHg)	118 ± 0.2	129 ± 0.5	< 0.0001
HDL cholesterol (mg/dL)	50 ± 0.3	51 ± 0.4	0.0161
Triglycerides (mg/dL)	134 ± 2.0	164 ± 3.1	< 0.0001
Waist circumference (cm)	91 ± 0.2	95 ± 0.4	< 0.0001
HOMA1R score	2.5 ± 0.1	3.9 ± 0.2	< 0.0001
NAFLD prevalence			
% with any NAFLD	34.5	42.2	< 0.0001
% with mild NAFLD	13.6	13.3	
% with moderate NAFLD	14.2	19.4	
% with severe NAFLD	6.8	9.4	

**Table 2**

Logistic regression of CKD on prevalent NAFLD as detected by ultrasound in the whole cohort of NHANES participants.

Regression Models	OR	95% CI	p-value
Unadjusted model	1.47	1.29–1.67	<0.0001
Model 1			
<i>adjusted for age, race, and sex</i>	1.21	1.04–1.40	0.014
Model 2			
<i>adjusted for age, race, sex, history of hypertension or diabetes, systolic BP, waist circumference, triglycerides, HDL cholesterol, and HOMA-IR</i>	1.04	0.88–1.23	0.64

**Table 3**

Logistic regression of CKD on prevalent NAFLD, stratified by diabetes status

Regression Models	Subjects without diabetes			Subjects with diabetes		
	OR	95% CI	p-value	OR	95% CI	p-value
Unadjusted model	1.40	1.22–1.61	<0.0001	1.08	0.66–1.76	0.75
Model 1						
<i>adjusted for age, race, and sex</i>	1.20	1.03–1.41	0.022	0.89	0.52–1.52	0.67
Model 2						
<i>adjusted for age, race, sex, history of hypertension or diabetes, systolic BP, waist circumference, triglycerides, HDL cholesterol, and HOMA-IR</i>	1.07	0.90–1.27	0.47	0.58	0.32–1.06	0.47