Title

Investigating the Association between Steatotic Liver Disease and CKD in a Nationally Representative Sample

Journal

Kidney360, 5(12)

ISSN

2641-7650

Authors

Lai, Mason
Lai, Jennifer C
Allegretti, Andrew S
et al.

Publication Date

2024-12-01

DOI

10.34067/kid.0000000569

Peer reviewed

Investigating the Association between Steatotic Liver Disease and CKD in a Nationally Representative Sample

Mason Lai[1], *Jennifer C. Lai*[1], *Andrew S. Allegretti*[2], *Kavish R. Patidar*[3,4], *and Giuseppe Cullaro*[1]

Key Points

- CKD is more common among those with steatotic liver disease compared with those without liver disease in the United States.
- Higher degrees of liver fibrosis are associated with greater prevalence of CKD independent of other common risk factors of kidney disease.

Abstract

Background Steatotic liver disease (SLD) and CKD are common conditions that are strongly associated. Yet, there is a paucity of data regarding the prevalence of this overlap and the factors that may drive its occurrence.

Methods Using the National Health and Nutrition Examination Survey, we examined trends among adult participants from 2005 to 2020 that defined SLD using the Fatty Liver Index. We completed correlative analyses among adult participants from 2017 to 2020 that defined SLD on the basis of FibroScan results. We used multivariable survey-weighted binomial generalized linear models to determine the factors that were associated with CKD, defined as eGFR <60 or urine albumin-creatinine ratio >30.

Results Among the 76,496 participants included in trend analyses, the estimated prevalence of CKD was 15.7% (95% confidence interval [CI], 15.2% to 16.2%) and SLD was 42.3% (95% CI, 41.4% to 43.2%). As compared with those without SLD, those with SLD had a significantly higher estimated prevalence of CKD (SLD, 15.7%; 95% CI, 14.9% to 16.5%; versus no SLD, 11.2%; 95% CI, 10.7% to 11.7%). In multivariate analyses of 3667 participants who underwent FibroScan and had SLD defined using the Fatty Liver Index, adjusting for control and presence of diabetes mellitus, hypertension, and hyperlipidemia/dyslipidemia, compared with those with normal liver stiffness, those with moderate scarring (F2) had similar odds of CKD (1.53; 95% CI, 0.91 to 2.56), those with severe scarring (F3) had higher odds of CKD (2.28; 95% CI, 1.20 to 4.32), and those with cirrhosis had higher odds of CKD (2.21; 95% CI, 1.13 to 4.32).

Conclusions Our findings highlight that CKD is common among patients with SLD and that higher degrees of hepatic fibrosis are associated with CKD independent of other comorbidities of the metabolic syndrome.

Kidney360 5: 1844–1852, 2024. doi: https://doi.org/10.34067/KID.0000000569

Introduction

Steatotic liver disease (SLD) and CKD are common diseases that have important clinical implications. In the United States, it is estimated that 24%–48% have SLD and 10%–15% have CKD—clearly, these are frequent problems that drive substantial morbidity and mortality, especially at a population level.[1,2] Several recent studies have highlighted an association between these two conditions—an association that seems to be independent of confounding diseases (*e.g.*, diabetes mellitus [DM] and

[1]Department of Medicine, University of California San Francisco, San Francisco, California
[2]Division of Nephrology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
[3]Section of Gastroenterology, Department of Medicine, Baylor College of Medicine, Houston, Texas
[4]Michael E. DeBakey Veterans Affairs Medical Center, Houtson, Texas

Correspondence: Dr. Giuseppe Cullaro, email: gc2576@cumc.columbia.edu

Received: February 8, 2024 **Accepted:** August 23, 2024
Published Online Ahead of Print: September 5, 2024

hypertension [HTN]).[3–5] Despite this preliminary understanding, the national estimates of the overlap of these diseases are lacking; a shortcoming that represents a critical need.

This need is critical because the treatment of SLD is rapidly evolving. These include targets of metabolism and lipotoxicity, insulin resistance, and anti-inflammatory and antifibrotic pathways.[6] Furthermore, many of these pathways have been implicated in the development and progression of CKD.[7] For example, recently, it has been highlighted that PNPLA3 mutations may play an independent role in CKD—the PNPLA3 I148M variant is a risk factor of CKD, independent of other kidney risk factors, and among cohorts with SLD, those with high-risk alleles were significantly more likely to have CKD.[4,8–11] With several drugs that target the PNPLA3 mutation (*e.g.*, AZD2693, NCT04483947) under development, a further understanding of the burden of CKD among patients with SLD and the factors that drive CKD among patients with SLD would inform the trial design and evaluation of this important comorbidity.

We harness the power of the National Health and Nutrition Examination Survey (NHANES) to (*1*) provide accurate prevalence estimates of the burden of CKD among people with and without SLD, (*2*) evaluate the changes in the burden of CKD among specific subgroups over time, and (*3*) provide exploratory correlative analyses to evaluate the factors that are most associated with CKD among those with SLD.

Methods

Data Source and Study Population

The NHANES is a continuous, multistage, nationally representative survey of the noninstitutionalized US civilian population.[4] These data, which are collected in 2-year intervals, represent a series of survey, laboratory, and imaging data. We divided our analyses into two parts: (*1*) trend analyses and (*2*) correlative analyses.

For the trend analyses, we compared the prevalence of specific diagnoses in the following intervals: 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016, and 2017–2020. The last time period is a 3.2-year span, because NHANES combined the 2017–2018 and shortened the 2019 to March 2020 data collection window due to the coronavirus disease 2019 pandemic.[4] We only included adult participants with completed laboratory components of the survey through the Mobile Examination Center (MEC), specifically urine albumin-creatinine ratios and serum creatinine (sCr). Participants who completed laboratory measurements and liver stiffness measurement through the MEC were randomly selected per NHANES protocols, and the appropriate multiyear MEC weights were used for all analyses.

For the correlative analysis, we used the 2017–2020 interval and included adult (18 years and older) participants with completed examination and laboratory components of the survey and who had laboratory evidence of SLD (as defined by Fatty Liver Index [FLI] ≥60). Specifically, we

Table 1. Unweighted characteristics among National Health and Nutrition Examination Survey participants with steatotic liver disease and who underwent FibroScan from 2017 to 2020

Characteristic	F0–F1, n=2,699[a]	F2, n=505[a]	F3, n=186[a]	F4, n=277[a]
CKD	484 (18)	126 (25)	57 (31)	94 (34)
eGFR	97 (80–112)	99 (78–109)	88 (69–105)	98 (76–110)
uACR	7 (5–14)	9 (5–19)	10 (6–25)	12 (6–30)
Female sex	1276 (47)	226 (45)	86 (46)	114 (41)
Age (yr)	51 (38–63)	55 (42–63)	60 (45–68)	58 (46–66)
History of hyperlipidemia	1228 (45)	236 (47)	98 (53)	137 (49)
Total cholesterol	189 (164–216)	185 (160–212)	175 (150–206)	173 (147–206)
LDL calculated	107 (85–130)	105 (83–124)	95 (68–121)	93 (73–121)
History of diabetes	549 (20)	164 (32)	81 (44)	115 (42)
Hemoglobin A1c	5.70 (5.40–6.10)	5.90 (5.50–6.60)	6.10 (5.50–7.20)	6.00 (5.60–6.80)
BMI	33 (30–37)	36 (32–41)	37 (33–42)	37 (32–45)
Waist circumference	109 (103–118)	116 (107–126)	120 (112–129)	122 (110–136)
Liver stiffness (kPa)	5.0 (4.2–5.8)	7.8 (7.3–8.4)	10.4 (9.9–11.0)	16.7 (13.6–24.5)
History of HTN	1201 (44)	265 (52)	110 (59)	170 (61)
SBP	123 (112–136)	126 (116–138)	127 (115–141)	126 (115–139)
Total grams alcohol per day	2 (0–8)	1 (0–6)	1 (0–6)	1 (0–7)
Race				
Asian	197 (7.3)	27 (5.3)	12 (6.5)	17 (6.1)
Black	712 (26)	138 (27)	52 (28)	64 (23)
Hispanic	695 (26)	136 (27)	46 (25)	72 (26)
Non-Hispanic White	954 (35)	183 (36)	69 (37)	110 (40)
Other	141 (5.2)	21 (4.2)	7 (3.8)	14 (5.1)
GGT	26 (18–40)	28 (20–44)	30 (20–57)	35 (22–71)
FLI	85 (73–94)	92 (82–98)	96 (89–99)	97 (88–99)

F0 denotes no liver fibrosis, F1 denotes minimal fibrosis, F2 denotes significant fibrosis, F3 denotes severe fibrosis, and F4 denotes cirrhosis. BMI, body mass index; eGFR, eGFR (2021 CKD Epidemiology Collaboration without race coefficient); FLI, Fatty liver Index; GGT, gamma-glutamyltransferase; HTN, hypertension; SBP, systolic BP; uACR, urine albumin-creatinine ratio.
[a]Percentage; median (interquartile range).

included those with completed vibration-controlled transient elastography with LSM values (Table 1). For both portions of the analyses, we followed recommended weighting procedures to maintain the representative nature of the sample.[12,13]

Predictors

We determined fibrosis in two ways. We used the LSM when FibroScan was available (*i.e.*, in the correlative analyses). We used the following LSM cutoffs: no fibrosis <7 kPa, minimal fibrosis ≥7 and <9.5 kPa, and advanced fibrosis ≥12 kPa.[14] For the trend analyses when FibroScan was not uniformly available, we defined fibrosis using the non-alcoholic fatty liver disease Fibrosis Score (NFS): no fibrosis <−1.455, mild fibrosis ≥−1.455 and <−0.675, and advanced fibrosis ≥−0.675.[15] We defined SLD using FLI ≥60.[16]

Outcomes

The primary outcome of the correlative and trend analyses was CKD. This was defined by either a urine albumin-creatinine ratio (uACR) ≥30 mg/g or an eGFR of ≤60 ml/min/1.73 m^2,[13] including those with eGFR <15 (as proxy for dialysis, as this is not reported directly within NHANES). To calculate eGFR, we used the 2021 race-free sCr CKD Epidemiology Collaboration formula.[15] The measurement of sCr and urine albumin-creatinine ratio was standardized per NHANES protocols.

Covariates

We defined other covariates similarly for both the correlative and trend analyses. Covariate selection was focused on components of the metabolic syndrome and sociodemographic factors. We used age, sex, and race as self-reported by participants during in-home interviews. Diabetes was included as a combination of historical variables (*i.e.*, have you ever been diagnosed with diabetes?) and a continuous variable (*i.e.*, hemoglobin A1c). We defined control of diabetes as A1c<7.0. HTN was included as a combination of historical variables (*i.e.*, have you ever been diagnosed with HTN?) and a continuous variable (*i.e.*, systolic BP). Control of HTN was defined as systolic BP ≤130. Hyperlipidemia was included as a combination of historical variables (*i.e.*, have you ever been diagnosed with high cholesterol?) and a continuous variable (*i.e.*, LDL, calculated).[17] Control of hyperlipidemia was defined as LDL calculated <100. Body mass index was included as kg/m^2.

Subgroups

We completed the trend analyses in several key subgroups. We compared the trend in the weighted prevalence of CKD by FLI-defined steatosis and NFS-defined fibrosis. We then repeated these analyses by steatosis, diabetes history, HTN history, and hyperlipidemia history.

Statistical Analyses

All analyses used survey procedures to account for the complex, cluster-stratified design of NHANES. Examination sampling weights provided by NHANES for all study periods were used to generate nationally representative estimates. The variance was estimated by Taylor series linearization to derive accurate standard errors and confidence intervals (CIs).

For the trend analyses, we estimated the prevalence-weighted means and percentages for demographic factors in 2-year survey cycles. Temporal trends for CKD among those with SLD were assessed with the use of weighted binomial generalized linear regression models by year. We tested the significance of these temporal trends with Wald tests.

For the correlative analyses, we used generalized linear models with a binomial family and logit-link that incorporated survey weights to ensure accurate estimation in the presence of a complex sampling structure. We used the MEC weights provided by NHANES given our analyses depended on these variables and followed recommended subgroup procedures. We completed both univariable and multivariable analyses. This was repeated in a set of sensitivity analyses, breaking down the CKD outcome into eGFR ≤60 and uACR ≥30. Odds ratios and their corresponding 95% CIs were reported. A statistical significance cutoff of $P < 0.05$ was used for all analyses.

All analyses were completed in R version 4.3.1 (Beagle Scouts), with several packages being instrumental: survey and gtsummary.[18,19] This study was approved by the National Center for Health Statistics Institutional Review Board, and all participants provided informed consent. The study was conducted in accordance with the Declaration of Helsinki.

Results

Trend Analyses

Overall

Among the 76,496 participants included in the trend analyses, the weighted mean of FLI was 49.3 (95% CI, 48.6 to 49.9) and NFS was −2.2 (95% CI, −2.2 to −2.2). The weighted mean eGFR was 100.0 (95% CI, 99.5 to 100.5), and the weighted median uACR was 7.1 (95% CI, 7.0 to 7.2). The estimated prevalence of CKD was 15.7% (95% CI, 15.2% to 16.2%), SLD 42.3% (95% CI, 41.4% to 43.2%), diabetes history 9.1% (95% CI, 8.7% to 9.4%), HTN history 29.9% (95% CI, 29.1% to 30.8%), and dyslipidemia history 31.9% (95% CI, 31.1% to 32.6%). The prevalence of SLD rose slightly from 2005 to 2020, ranging from 40.3% (95% CI, 38.1 to 42.5) to 45.5% (95% CI, 43.3% to 47.8%), reaching its peak in the 2017 to March 2020 period (Supplemental Figure 5).

Prevalence and Trends by SLD and Fibrosis Categories

As compared with those without SLD (estimated prevalence 11.2%, 95% CI, 10.7% to 11.8%), we found that those with SLD and no to minimal fibrosis had similar levels of CKD (estimated prevalence 10.1%; 95% CI, 9.4% to 10.9%), and those with SLD and advanced fibrosis (estimated prevalence 31.4%; 95% CI, 29.6% to 33.1%) had higher estimates of CKD. We show the biannual estimated prevalence of CKD by SLD and fibrosis category (*i.e.*, no SLD, SLD/no fibrosis, SLD/minimal fibrosis, and SLD/advanced fibrosis) in Figure 1. The prevalence of CKD was roughly stable across participants without SLD and those with SLD and no fibrosis (Wald test $P > 0.05$). By contrast, prevalence of CKD

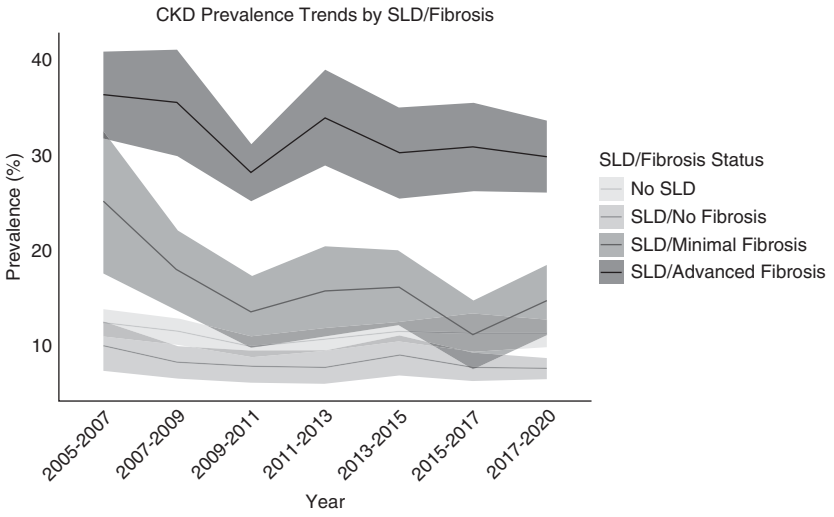

Figure 1. Prevalence of CKD in the United States by SLD and fibrosis category from 2005 to March 2020. SLD, steatotic liver disease.

in those with mild fibrosis or advanced fibrosis as estimated by FLI seemed to decrease over time (Wald test $P < 0.05$).

Prevalence and Trends by SLD, Fibrosis, and Diabetes History

Among those with SLD, 15.8% (95% CI, 14.8% to 16.9%) had comorbid diabetes. Those with worse degrees of fibrosis and comorbid diabetes had higher burden of CKD. Those with SLD and no to minimal fibrosis without diabetes had the lowest burden of CKD (8.8%; 95% CI, 8.1% to 9.6%). Those with SLD and no to minimal fibrosis and comorbid diabetes (26.6%; 95% CI, 23.3% to 30.0%) had similar rates of CKD as those with advanced fibrosis but without diabetes (24.8%; 95% CI, 22.7% to 27.0%). Participants with both advanced fibrosis and comorbid diabetes had the highest rates of CKD (38.9%; 95% CI, 36.4% to 41.4%).

We demonstrate the biannual estimated prevalence of CKD by SLD, fibrosis, and diabetes in Figure 2. Among participants with both SLD and DM, those with advanced fibrosis and uncontrolled DM seemed to have higher rates of CKD compared with those with no to minimal fibrosis and controlled DM (Supplemental Figure 1). CKD change by year was not statistically significant ($P > 0.05$).

Prevalence and Trends by SLD, Fibrosis, and HTN History

Among those with SLD, 35.8% (95% CI, 33.0% to 38.8%) had comorbid HTN. Worsening degrees of fibrosis and comorbid HTN showed a stepwise relationship with prevalence of CKD. Those with SLD and no to minimal fibrosis without HTN had the lowest burden of CKD (6.6%; 95% CI, 5.9% to 7.3%), followed by those with SLD with no to minimal fibrosis and comorbid HTN (16.9%; 95% CI, 15.5% to 18.3%). Of participants with advanced fibrosis but without HTN, 20.7% had CKD (95% CI, 18.2% to 23.2%), and 37.3% (95% CI, 35.2% to 39.5%) of those with advanced fibrosis and comorbid HTN had CKD.

We demonstrate the biannual estimated prevalence of CKD among those with SLD by fibrosis and HTN in Figure 3.

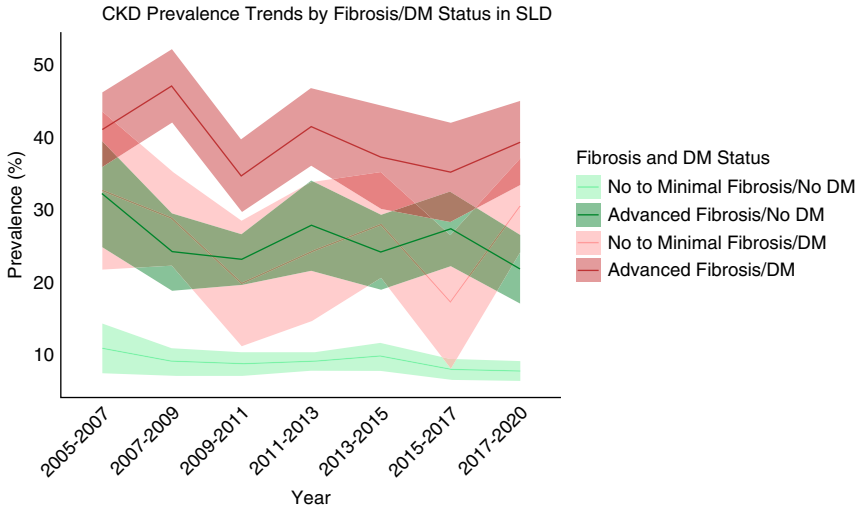

Figure 2. Prevalence of CKD in the United States and SLD, fibrosis category, and diabetes from 2005 to March 2020. DM, diabetes mellitus.

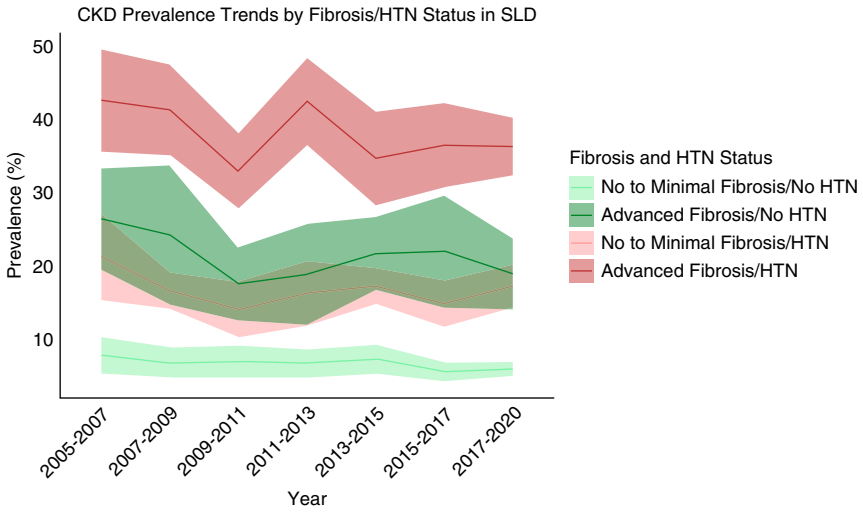

Figure 3. Prevalence of CKD in the United States and SLD, fibrosis category, and HTN from 2005 to March 2020. HTN, hypertension.

Among participants with both SLD and HTN, those with advanced fibrosis and uncontrolled HTN seemed to have higher rates of CKD compared with those with no to minimal fibrosis and controlled HTN (Supplemental Figure 2). CKD change by year was not statistically significant ($P > 0.05$).

Prevalence and Trends by SLD, Fibrosis, and Dyslipidemia History

Among those with SLD, 39.4% had comorbid dyslipidemia (95% CI, 37.3% to 41.6%). Worsening degrees of fibrosis and comorbid dyslipidemia showed a stepwise relationship with prevalence of CKD. Those with SLD and no to minimal fibrosis but without dyslipidemia had the lowest burden of CKD (8.9%; 95% CI, 8.1% to 9.6%), followed by those with SLD with no to minimal fibrosis and comorbid dyslipidemia (12.5%; 95% CI, 11.1% to 13.8%). Of participants with advanced fibrosis but without dyslipidemia, 27.5% had CKD (95% CI, 25.0% to 30.1%), and 34.1% (95% CI, 31.8% to 36.4%) of those with advanced fibrosis and comorbid dyslipidemia had CKD.

We demonstrate the biannual estimated prevalence of CKD by fibrosis and dyslipidemia in Figure 4. Among participants with both SLD and dyslipidemia, those with advanced fibrosis and uncontrolled dyslipidemia seemed to have higher rates of CKD compared with those with no to minimal fibrosis and controlled dyslipidemia (Supplemental Figure 3). CKD change by year was not statistically significant ($P > 0.05$).

Correlative Analyses

From 2017–2020, 3667 participants with SLD underwent FibroScan and were included in the following analyses. In weighted univariate analyses, the factors that were significantly associated with CKD are listed in

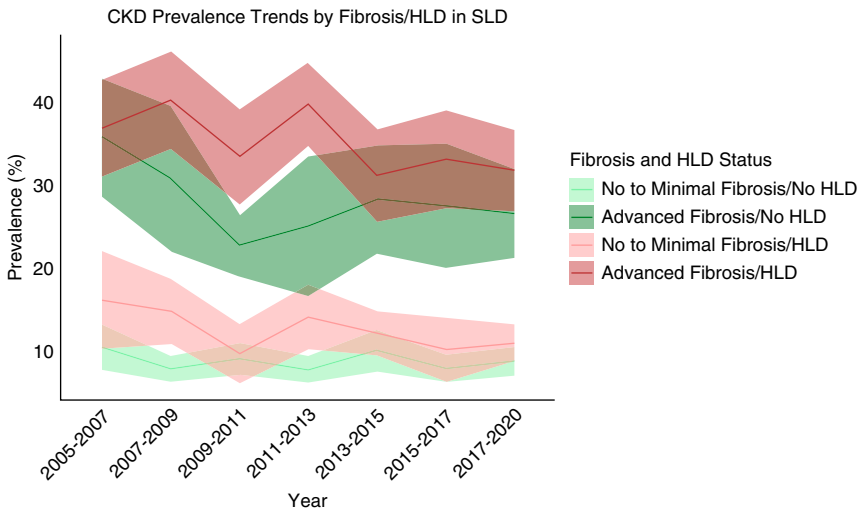

Figure 4. Prevalence of CKD in the United States and SLD, fibrosis category, and dyslipidemia from 2005 to March 2020. HLD, hyperlipidemia/dyslipidemia.

Table 2. Notably, in univariate analyses, the liver stiffness category was significantly associated with CKD. Similarly, in multivariable analyses, worse liver stiffness categories (F3 and F4) were both associated with an approximately two-fold higher odds of CKD (Table 2), independent of DM control, HTN control, hyperlipidemia/dyslipidemia control, as well as sociodemographic factors. In addition, participants with SLD who identified as Black had higher odds of CKD.

In exploratory subgroup analyses in individuals with SLD and DM, HTN, or hyperlipidemia/dyslipidemia, we examined commonly used medication classes for association with CKD. We did not find evidence that use of specific medication classes were associated with decreased rates of CKD (Supplemental Tables 1–3).

In additional sensitivity analyses, we separated our outcome of CKD into its components, namely eGFR <60 and uACR >30. Liver stiffness category was significantly associated with CKD by eGFR in univariate analysis but was NS in multivariate analyses (Supplemental Table 6). The liver stiffness category was significantly associated with CKD by uACR in both univariate and multivariate analyses (Supplemental Table 7).

Discussion

In this nationally representative sample, we inform the previously highlighted association between SLD and CKD.[3,5,10,20–24] Using FLI ≥60 to define SLD, we found the estimated prevalence of SLD to be 42.3%. We estimated CKD among those with SLD to be 13.7%. Our trend analyses of CKD prevalence over time highlight that despite the emergence of treatments that may prevent CKD (*e.g.*, sodium-glucose co-transporter 2 inhibitors and angiotensin-converting enzyme inhibitors), there have not been significant changes in the prevalence of CKD over time among those with SLD. Importantly, we highlight that the association between SLD and CKD is associated with underlying fibrosis and is independent of frequent confounders—diabetes, HTN, and dyslipidemia. When considered in the context of the global burden of SLD, we believe these data are critical—informing the relationship between these frequently encountered diseases and generating hypotheses for potential opportunities to prevent their occurrence.

Our study highlights that CKD is common among patients with SLD, present in nearly one in every six patients, which, when contextualized to the 24%–48% of all North

Table 2. Factors associated with CKD in weighted univariable and multivariable logistic regression, among National Health and Nutrition Examination Survey participants with steatotic liver disease from 2017–2020

Characteristic	Univariable			Multivariable		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Female sex	1.22	0.96 to 1.54	0.10	1.27	0.90 to 1.79	0.14
Age (per 10 yr)	1.62	1.52 to 1.74	<0.001	1.39	1.21 to 1.59	<0.001
BMI	1.02	1.01 to 1.04	0.002	0.98	0.95 to 1.01	0.2
FibroScan category						
F0–F1 (ref)	—	—		—	—	
F2	2.02	1.57 to 2.61	<0.001	1.53	0.91 to 2.56	0.10
F3	3.21	2.09 to 4.91	<0.001	2.28	1.20 to 4.32	0.017
F4	2.88	1.85 to 4.48	<0.001	2.21	1.13 to 4.32	0.025
Race						
Asian	1.18	0.85 to 1.64	0.3	1.24	0.83 to 1.87	0.3
Black	1.69	1.27 to 2.24	0.001	1.90	1.30 to 2.79	0.004
Hispanic	0.94	0.71 to 1.23	0.6	1.13	0.81 to 1.58	0.4
Non-Hispanic White	—	—		—	—	
Other	1.15	0.76 to 1.74	0.5	1.04	0.55 to 1.96	>0.9
Diabetes						
None	—	—		—	—	
Controlled DM	3.73	2.91 to 4.79	<0.001	2.42	1.45 to 4.04	0.004
Not controlled DM	9.44	7.10 to 12.5	<0.001	4.11	2.56 to 6.60	<0.001
HTN						
None	—	—		—	—	
Controlled HTN	3.53	2.70 to 4.61	<0.001	2.02	1.22 to 3.36	0.012
Not controlled HTN	6.09	4.80 to 7.72	<0.001	2.55	1.69 to 3.83	<0.001
HLD						
None	—	—		—	—	
Controlled HLD	3.35	2.52 to 4.44	<0.001	0.86	0.51 to 1.44	0.5
Not controlled HLD	1.28	0.86 to 1.91	0.2	0.72	0.44 to 1.16	0.2

Outcome CKD defined as eGFR ≤60 and/or urine albumin-creatinine ratio ≥30.
Steatotic liver disease as defined by Fatty Liver Index ≥60. F0 denotes no liver fibrosis, F1 denotes minimal fibrosis, F2 denotes significant fibrosis, F3 denotes severe fibrosis, and F4 denotes cirrhosis.
BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HLD, hyperlipidemia/dyslipidemia; HTN, hypertension; OR, odds ratio.

American adults who have SLD, reinforces the critical need to understand this association better.[1] We expand on this by demonstrating that the prevalence of CKD is greater with higher degrees of underlying fibrosis. For instance, we demonstrate that among those with SLD, the estimated prevalence of CKD ranges from 10.1% among those with no to minimal fibrosis to 31.3% among those with advanced fibrosis. These findings align with those found in the nonalcoholic steatohepatitis Clinical Research Network, but why does this occur?[24] We offer two hypotheses: (*1*) patients with increasing liver fibrosis have likely had SLD and its comorbidities for both a greater duration and a greater severity, thereby accumulating greater kidney damage over time, and (*2*) there may be profibrotic hepatic pathways that also have implications for nephrologic fibrosis. For example, previous studies have highlighted the potential role of PNPLA3 mutations[8,10,11,25] and the thyroid hormone receptor β[26] in the development of CKD, both pathways with implications for the development of hepatic fibrosis among patients with SLD. We believe our data are hypothesis generating because these two hypotheses can be tested (*1*) in longitudinal cohorts that quantify the metabolic syndrome and steatohepatitis over time, and (*2*) in a secondary analysis of prior clinical trials that attempted to treat these profibrotic pathways and investigate the effect of these treatments on eGFR over time during the study period.

Our data also demonstrate that the effect of hepatic fibrosis is independent of common comorbidities associated with CKD (*i.e.*, HTN, diabetes, obesity, and hyperlipidemia). In our correlative analyses, we demonstrate that worsening degrees of the LSM was significantly associated with a higher prevalence CKD, independent of confounders. This association was also evident in our trend analyses. For example, regardless of diabetes history and control, HTN status and control, or dyslipidemia status and control, we demonstrate that the estimated prevalence of CKD is greater with the greater estimated prevalence of hepatic fibrosis. In our sensitivity analyses, the association between liver fibrosis and CKD seems to be more influenced by albuminuria than eGFR. Further investigation is warranted as these outcomes reflect different aspects of kidney health. Collectively, these data highlight that the association between hepatic fibrosis and CKD is not fully explained by the increased burden of these common comorbidities among patients with hepatic fibrosis.

The trend analyses demonstrate that among those with SLD and minimal or advanced fibrosis, CKD prevalence has decreased. One possibility is this might reflect an increase in the use of newer medications targeting the metabolic syndrome and comorbidities, such as GLP1 agonists or SGLT2 inhibitors.[27] There were no significant changes over time when analyzed by SLD and comorbidity subgroups. Collectively, these data highlight the high prevalence of CKD among patients with SLD, which suggests it is an enduring complication that warrants intervention. That said, why it is increasing in the general population but not in the SLD population remains unanswered.[28]

This study has several limitations. First, NHANES is a cross-sectional study; therefore, no comments or investigations into duration or comorbidity changes over time can be made. However, our study design allows a commentary into the prevalence of these conditions in a nationally representative sample. Second, some variables are self-reported. This can lead to inaccurate quantification of some covariates, such as reported history of a comorbidity. To balance this, wherever possible, we included both the reported history of a diagnosis (*e.g.*, history of diabetes) and the laboratory values that correspond with the diagnosis (*e.g.*, A1c). Third, and most importantly, our analyses hinge on surrogates of SLD (*i.e.*, FLI) and hepatic fibrosis (*i.e.*, LSM and NFS). Although imperfect, these are well-validated metrics with good operating characteristics and they allowed us to determine the degree of steatosis and hepatic fibrosis at a population level.[16,17,29–32]

Despite these limitations, we believe that our data provide important prevalence estimates regarding the burden of CKD among patients with SLD. Our findings highlight that CKD is common among patients with SLD and that hepatic fibrosis is independently associated with CKD, irrespective of other comorbidities of the metabolic syndrome.

Disclosures

Disclosure forms, as provided by each author, are available with the online version of the article at http://links.lww.com/KN9/A664.

Funding

G. Cullaro: National Institutes of Health (K23DK131278) and American Association for the Study of Liver Diseases (Clinical, Translational, and Outcomes Research Award). A.S. Allegretti: National Institutes of Health (K23 DK128567). J.C. Lai: Liver Center, University of California, San Francisco (P30 DK026743).

Author Contributions

Conceptualization: Giuseppe Cullaro.
Formal analysis: Giuseppe Cullaro, Mason Lai.
Funding acquisition: Giuseppe Cullaro, Kavish R. Patidar.
Investigation: Andrew S. Allegretti, Giuseppe Cullaro, Mason Lai, Kavish R. Patidar.
Methodology: Giuseppe Cullaro, Jennifer C. Lai, Mason Lai.
Resources: Jennifer C. Lai.
Supervision: Giuseppe Cullaro, Kavish R. Patidar.
Visualization: Mason Lai.
Writing – original draft: Giuseppe Cullaro, Mason Lai.
Writing – review & editing: Andrew S. Allegretti, Giuseppe Cullaro, Jennifer C. Lai, Mason Lai, Kavish R. Patidar.

Data Sharing Statement

Previously published data were used for this study. NHANES Data.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A663.

Supplemental Figure 1. Prevalence of CKD in the United States and steatotic liver disease, fibrosis category, and diabetes control from 2005 to March 2020. SLD, steatotic liver disease; diabetes control defined as A1c ≤7.0.

Supplemental Figure 2. Prevalence of CKD in the United States and steatotic liver disease, fibrosis category, and HTN control from 2005 to March 2020. SLD, steatotic liver disease; hypertension control defined as systolic BP ≤130.

Supplemental Figure 3. Prevalence of CKD in the United States and steatotic liver disease, fibrosis category, and dyslipidemia

control from 2005 to March 2020. SLD, steatotic liver disease; dyslipidemia control defined as LDLc <100.

Supplemental Figure 4. Makeup of CKD outcome prevalence over time by SLD/fibrosis category in NHANES 2005–2020.

Supplemental Figure 5. SLD prevalence trends in NHANES 2005 to March 2020.

Supplemental Table 1. Factors and DM medications associated with CKD in weighted univariable and multivariable logistic regression, among NHANES participants with SLD and DM from 2017 to 2020.

Supplemental Table 2. Factors and HTN medications associated with CKD in weighted univariable and multivariable logistic regression, among NHANES participants with SLD and HTN from 2017 to 2020.

Supplemental Table 3. Factors and HLD medications associated with CKD in weighted univariable and multivariable logistic regression, among NHANES participants with SLD and HLD from 2017 to 2020.

Supplemental Table 4. Weighted estimates of CKD prevalence by comorbidity status and SLD/fibrosis category.

Supplemental Table 5. Weighted estimates of eGFR <60 and uACR >30 among those with SLD and CKD in NHANES 2005–2020.

Supplemental Table 6. Factors associated with CKD (eGFR ≤60) in weighted univariable and multivariable logistic regression, among NHANES participants with SLD from 2017 to 2020.

Supplemental Table 7. Factors associated with CKD (uACR ≥30) in weighted univariable and multivariable logistic regression, among NHANES participants with SLD from 2017 to 2020.

Supplemental Table 8. Univariate and multivariate weighted estimates of eGFR difference in NHANES 2017–2020 participants with SLD.

References

1. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. *J Hepatol.* 2023; 79(2):516–537. doi:10.1016/j.jhep.2023.03.017
2. Kibria GMA, Crispen R. Prevalence and trends of chronic kidney disease and its risk factors among US adults: an analysis of NHANES 2003-18. *Prev Med Rep.* 2020;20:101193. doi: 10.1016/j.pmedr.2020.101193
3. Targher G, Bertolini L, Rodella S, Lippi G, Zoppini G, Chonchol M. Relationship between kidney function and liver histology in subjects with nonalcoholic steatohepatitis. *Clin J Am Soc Nephrol.* 2010;5(12):2166–2171. doi:10.2215/CJN.05050610
4. Akinbami L, Chen T-C, Davy O, et al. National Health and Nutrition Examination Survey, 2017–March 2020 prepandemic file: sample design, estimation, and analytic guidelines. *Vital Health Stat 1.* 2022;(190):1–36. PMID: 35593699
5. Byrne CD, Targher G. NAFLD as a driver of chronic kidney disease. *J Hepatol.* 2020;72(4):785–801. doi:10.1016/j.jhep.2020.01.013
6. Tilg H, Byrne CD, Targher G. NASH drug treatment development: challenges and lessons. *Lancet Gastroenterol Hepatol.* 2023;8(10):943–954. doi:10.1016/S2468-1253(23)00159-0
7. Targher G, Byrne CD. Non-alcoholic fatty liver disease: an emerging driving force in chronic kidney disease. *Nat Rev Nephrol.* 2017;13(5):297–310. doi:10.1038/nrneph.2017.16
8. Mantovani A, Taliento A, Zusi C, et al. *PNPLA3* I148M gene variant and chronic kidney disease in type 2 diabetic patients with NAFLD: clinical and experimental findings. *Liver Int.* 2020; 40(5):1130–1141. doi:10.1111/liv.14419
9. D'Erasmo L, Baratta F, Di Costanzo A, et al. Role of NAFLD-associated genetic variants on renal function in patients with non-alcoholic fatty liver disease. *J Hepatol.* 2022;77:S162. doi: 10.1016/S0168-8278(22)00703-6
10. Targher G, Mantovani A, Alisi A, et al. Relationship between PNPLA3 rs738409 polymorphism and decreased kidney function in children with NAFLD. *Hepatology.* 2019;70(1):142–153. doi: 10.1002/hep.30625
11. Musso G, Cassader M, Gambino R. PNPLA3 rs738409 and TM6SF2 rs58542926 gene variants affect renal disease and function in nonalcoholic fatty liver disease. *Hepatology.* 2015; 62(2):658–659. doi:10.1002/hep.27643
12. Johnson CL, Paulose-Ram R, Ogden CL, et al. National Health and Nutrition Examination Survey: analytic guidelines, 1999-2010. *Vital Health Stat 2.* 2013;(161):1–24. PMID: 25090154
13. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63(5):713–735. doi: 10.1053/j.ajkd.2014.01.416
14. Tsochatzis EA, Gurusamy KS, Ntaoula S, Cholongitas E, Davidson BR, Burroughs AK. Elastography for the diagnosis of severity of fibrosis in chronic liver disease: a meta-analysis of diagnostic accuracy. *J Hepatol.* 2011;54(4):650–659. doi:10.1016/j.jhep.2010.07.033
15. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. *New Engl J Med.* 2021;385(19):1737–1749. doi:10.1056/NEJMoa2102953
16. Bedogni G, Bellentani S, Miglioli L, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. *BMC Gastroenterol.* 2006;6:33. doi:10.1186/1471-230x-6-33
17. Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. *Hepatology.* 2007;45(4):846–854. doi:10.1002/hep.21496
18. Lumley T. Analysis of complex survey samples. *J Stat Softw.* 2004; 9(8):1–19. doi:10.18637/jss.v009.i08
19. Sjoberg D, Whiting K, Curry M, Lavery J, Larmarange J. Reproducible summary tables with the gtsummary package. *R J.* 2021;13(1):570–580. doi:10.32614/RJ-2021-053
20. Targher G, Bertolini L, Rodella S, et al. Non-alcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and proliferative/laser-treated retinopathy in type 2 diabetic patients. *Diabetologia.* 2008;51(3): 444–450. doi:10.1007/s00125-007-0897-4
21. Sirota JC, McFann K, Targher G, Chonchol M, Jalal DI. Association between nonalcoholic liver disease and chronic kidney disease: an ultrasound analysis from NHANES 1988–1994. *Am J Nephrol.* 2012;36(5):466–471. doi:10.1159/000343885
22. Mantovani A, Petracca G, Beatrice G, et al. Non-alcoholic fatty liver disease and risk of incident chronic kidney disease: an updated meta-analysis. *Gut.* 2022;71(1):156–162. doi:10.1136/gutjnl-2020-323082
23. Loomba R, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol.* 2013;10(11):686–690. doi:10.1038/nrgastro.2013.171
24. Sanyal AJ, Van Natta ML, Clark J, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver disease. *New Engl J Med.* 2021;385(17):1559–1569. doi:10.1056/NEJMoa2029349
25. Marzuillo P, Di Sessa A, Guarino S, et al. Nonalcoholic fatty liver disease and eGFR levels could be linked by the *PNPLA3* I148M polymorphism in children with obesity. *Pediatr Obes.* 2019; 14(10):e12539. doi:10.1111/ijpo.12539
26. Copur S, Yavuz F, Kanbay M. Thyroid hormone Beta receptor agonists for treatment of kidney disease: a promising agent? *Eur J Clin Invest.* 2023;53(5):e13939. doi:10.1111/eci.13939
27. Fang M, Wang D, Coresh J, Selvin E. Trends in diabetes treatment and control in U.S. Adults, 1999–2018. *New Engl J Med.* 2021; 384(23):2219–2228. doi:10.1056/NEJMsa2032271
28. Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. *Lancet.* 2017;389(10075):1238–1252. doi:10.1016/s0140-6736(16)32064-5
29. Koehler EM, Schouten JNL, Hansen BE, Hofman A, Stricker BH, Janssen HLA. External validation of the fatty liver index for identifying nonalcoholic fatty liver disease in a population-based study. *Clin Gastroenterol Hepatol.* 2013;11(9):1201–1204. doi: 10.1016/j.cgh.2012.12.031

30. Cao Y-T, Xiang L-L, Qi F, Zhang Y-J, Chen Y, Zhou X-Q. Accuracy of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) for assessing steatosis and fibrosis in non-alcoholic fatty liver disease: a systematic review and meta-analysis. *EClinicalMedicine*. 2022;51:101547. doi:10.1016/j.eclinm.2022.101547
31. Sasso M, Miette V, Sandrin L, Beaugrand M. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan®. *Clin Res Hepatol Gastroenterol*. 2012;36(1):13–20. doi:10.1016/j.clinre.2011.08.001
32. De Lédinghen V, Vergniol J, Capdepont M, et al. Controlled attenuation parameter (CAP) for the diagnosis of steatosis: a prospective study of 5323 examinations. *J Hepatol*. 2014;60(5):1026–1031. doi:10.1016/j.jhep.2013.12.018