

# Metabolic Dysfunction-Associated Steatotic Liver Disease and Liver Fibrosis are Associated with Advanced Cardiovascular-Kidney-Metabolic Syndrome in Chinese and US Populations

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**Purpose:** Despite the pathophysiologic overlap between metabolic dysfunction-associated steatotic liver disease (MASLD) and cardiovascular-kidney-metabolic (CKM) syndrome, MASLD has not been incorporated into the current CKM framework. This study examined the associations of MASLD and MASLD-related fibrosis with advanced CKM syndrome in Chinese and US populations.

**Patients and Methods:** We enrolled 6186 participants in a community-based cross-sectional study conducted in China, with validation utilizing the National Health and Nutrition Examination Survey (NHANES). Advanced CKM syndrome was defined as stages 3 and 4. Hepatic steatosis and fibrosis were assessed via vibration-controlled transient elastography. Multivariable logistic regression and restricted cubic spline (RCS) analyses were employed.

**Results:** Advanced CKM syndrome was present in 8.8% of the Chinese and 14.9% of the US populations. MASLD participants exhibited a significantly higher prevalence of advanced CKM than those without (China: 12.6% vs 6.4%; US: 21.5% vs 9.9%). In addition, participants with MASLD were associated with increased odds of advanced CKM (China: OR 2.06, 95% CI: 1.64–2.58; US: OR 1.60, 95% CI: 1.22–2.10; both  $P < 0.01$ ). Among participants with MASLD, advanced CKM syndrome was more prevalent in participants with fibrosis than without (China: 17.1% vs 11.2%; US: 28.4% vs 20.1%). MASLD-related fibrosis was also independently linked to higher odds of advanced CKM compared to non-fibrotic MASLD (China: OR 1.55, 95% CI: 1.09–2.18; US: OR 1.44, 95% CI: 1.01–2.05; both  $P < 0.05$ ). Furthermore, RCS analysis revealed a positive linear relationship of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) values with the prevalence of advanced CKM syndrome ( $P$  non-linear  $> 0.05$ ).

**Conclusion:** MASLD and MASLD-related fibrosis were significantly associated with a higher prevalence of advanced CKM syndrome, and higher CAP/LSM levels showed linear associations with advanced CKM syndrome in both Chinese and US populations. These findings support evaluating liver health (eg, CAP/LSM) when risk-stratifying CKM syndrome.

**Keywords:** advanced cardiovascular-kidney-metabolic syndrome, controlled attenuation parameter, fibrosis, liver stiffness measurement, metabolic dysfunction-associated steatotic liver disease

## Introduction

Cardiovascular-kidney-metabolic (CKM) syndrome is a progressive condition characterized by a complex multisystem interplay involving chronic kidney disease (CKD), cardiovascular disease (CVD), and metabolic risk factors.<sup>1</sup> The staging of CKM syndrome (0–4) is determined by its pathophysiological processes, providing an invaluable framework for risk stratification and the implementation of preventive strategies.<sup>2</sup> Research has recently indicated that approximately 15% of American adults display advanced CKM syndrome (stages 3–4),<sup>3,4</sup> highlighting its substantial public health burden. Consequently, as the prevalence of CKM syndrome components escalates globally, it becomes a major driver of morbidity and mortality,<sup>5</sup> necessitating critical clinical research to mitigate its severe implications.

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common condition closely linked to the increased incidence of metabolic disorders. Additionally, MASLD afflicts more than 30% of adults worldwide, constituting both the leading chronic liver disorder and a pivotal cardiometabolic determinant.<sup>6</sup> The new MASLD definition emphasizes the interplay between metabolic dysfunction and hepatic steatosis, thereby recognizing it not merely as an organ-specific disease but as a multisystem disorder.<sup>7</sup> A study examining the overlap and synergistic effects of five cardiometabolic risk factors on MASLD and liver fibrosis found that more than 80% of patients had three or more risk factors.<sup>8</sup> A greater number of cardiometabolic risk factors in MASLD, or the acquisition of these factors over time, is associated with a progressively elevated risk of subsequent adverse cardiorenal outcomes.<sup>9</sup> Furthermore, hepatic steatosis accelerates endothelial dysfunction, atherosclerosis, systemic inflammation, and renal injury, thus directly fueling the progression of CKD and CVD.<sup>10,11</sup>

A growing body of research highlights the strong association between MASLD and cardiovascular and kidney diseases. Notably, MASLD serves as an independent predictor of atherosclerotic cardiovascular disease (ASCVD) risk, thereby increasing morbidity and mortality rates.<sup>12,13</sup> Moreover, evidence from a large-scale Korean cohort study, which included 214,145 participants, revealed a robust correlation between MASLD and a heightened risk of developing CKD as well as abnormal proteinuria.<sup>14</sup> A meta-analysis encompassing nine observational studies and a total of 96,595 adults indicated that MASLD was linked to a 37% higher long-term risk of incident CKD,<sup>15</sup> emphasizing that hepatic steatosis is not merely a hepatic disorder but a multisystem metabolic condition. The recent conceptual framework of CARDIAL-MS (Cardio-Renal-DIAbetes-Liver-Metabolic Syndrome) integrates the liver into the cardio-renal-metabolic continuum, providing an actionable paradigm for clinical risk stratification and personalized prevention.<sup>16</sup>

Although it is well established that MASLD is linked to individual CKM components (eg, CKD, CVD),<sup>17</sup> a critical knowledge gap remains regarding the integrated relationship between MASLD and the progressive continuum of CKM syndrome as a unified entity. The American Heart Association (AHA) has acknowledged the pathophysiologic overlap between MASLD and CKM syndrome; however, the current CKM framework inadequately incorporates hepatic contributions across the disease continuum.<sup>1,18</sup> Furthermore, the progression from hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and significant liver fibrosis represents a pivotal transition point in the disease continuum, substantially amplifying the risk of both hepatic and extrahepatic complications, particularly adverse cardiovascular events.<sup>19</sup> However, whether the presence and severity of liver fibrosis confer an additional risk for advanced CKM syndrome beyond that of steatosis alone remains unclear. In addition, comprehensive investigations examining the prevalence and associations among MASLD, liver fibrosis, and advanced CKM syndrome are still lacking, especially in Chinese populations. Vibration-controlled transient elastography (VCTE)—which quantitatively evaluates hepatic steatosis via the controlled attenuation parameter (CAP) and fibrosis via liver stiffness measurement (LSM)—offers a superior, non-invasive approach.<sup>20</sup> Determining whether VCTE-based CAP and LSM provide additional prognostic value beyond existing CKM staging frameworks is therefore of critical clinical importance.

Therefore, this study aimed to: (1) investigate the prevalence of MASLD and associated fibrosis across the spectrum of CKM syndrome, while exploring potential overlapping correlations in Chinese and US cohorts; and (2) examine the associations of CAP, LSM, MASLD and MASLD-related fibrosis with the prevalence of advanced CKM syndrome. Ultimately, our goal was to provide evidence on whether MASLD and the degree of liver fibrosis should be incorporated into risk stratification of CKM syndrome.

## Materials and Methods

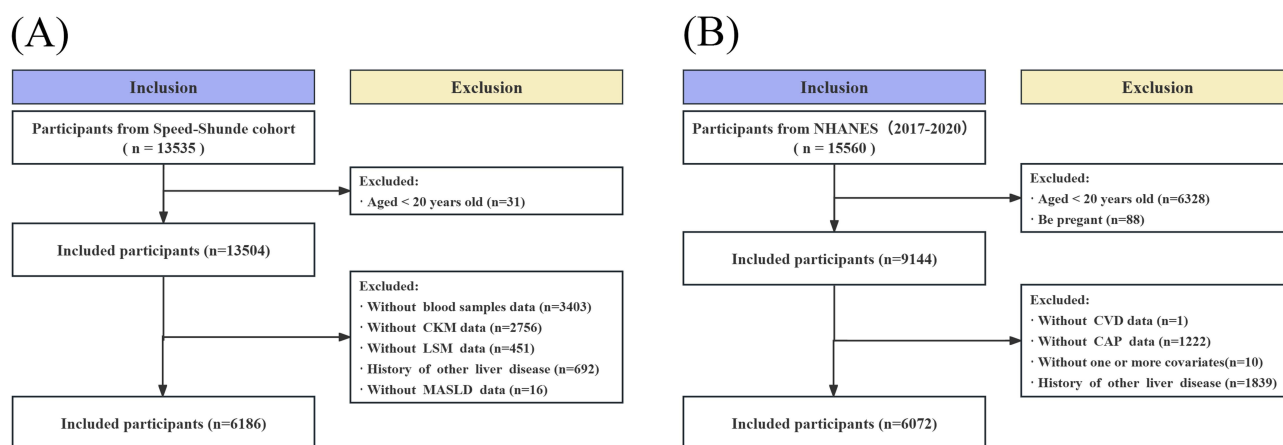
### Study Participants

We conducted a community-based, cross-sectional observational study in China (the Speed-Shunde Cohort). The study was registered in the Chinese Clinical Trial Registry (Registration Number: ChiCTR2100054130; Website: <http://www.chictr.org.cn/>). The research subjects were derived from a multistage stratified random sampling survey conducted across ten towns in Shunde District between November 2021 and September 2022.<sup>6,21,22</sup> Eligible residents were adults aged  $\geq 18$  years with  $\geq 6$  months' tenure in Shunde. Residents with acute illness, infection, trauma, or pregnancy were excluded from the study. A survey involving 13,535 participants was conducted. Exclusions were applied to individuals under 20 years old ( $n = 31$ ), those missing blood samples ( $n = 3403$ ), CKM data ( $n = 2756$ ), LSM data ( $n = 451$ ), those with other liver diseases ( $n = 692$ ), or a lack of data on MASLD ( $n = 16$ ). Consequently, a total of 6186 subjects were enrolled in the study (Figure 1A). The study was approved by the ethics committee of the Eighth Affiliated Hospital (The First People's Hospital of Shunde) of Southern Medical University, adhered to the 1975 Declaration of Helsinki's ethical guidelines (protocol 20211103 in China), and obtained written informed consent from all subjects.

The National Health and Nutrition Examination Survey (NHANES) was utilized as an external validation cohort to investigate potential differences between China and the United States. The NHANES is a systematic survey by the National Center for Health Statistics (NCHS) that collects demographic, clinical, laboratory, lifestyle, and self-reported health data. The present analysis utilized data from the 2017–2020 NHANES cycle, and all procedures adhered to the official survey guidelines. Notably, the study included 9144 individuals aged 20 or older who were not pregnant. Participants were excluded if they lacked data on CVD ( $n=1$ ), CAP data ( $n=1222$ ), covariates ( $n=10$ ), or had other liver diseases ( $n=1839$ ). Ultimately, 6072 participants were included in the analysis (Figure 1B).

### Data Collection

The Speed-Shunde cohort utilized a standardized protocol to collect comprehensive data on participants. Trained staff administered standardized questionnaires covering demographics, lifestyle, medical history, and medications. The questionnaire used was based on scales previously published by our team.<sup>6,22</sup> Detailed information about these scales can be found in our prior publications. Physical examinations were also conducted. Fasting blood specimens were obtained in the morning hours (8:00–10:00 AM) and analyzed thereafter for plasma glucose concentration, glycosylated hemoglobin, and lipid profiles. For participants without self-reported diabetes, a 2-hour oral 75g glucose tolerance test was performed, and 2-hour plasma glucose was measured. Additionally, random urine samples were tested for micro-albumin and creatinine using dipstick analysis. All biological samples were transported under cold chain conditions, centrifuged, and frozen at  $-20^{\circ}\text{C}$ .



**Figure 1** Flowchart of the study participants. **(A)** The Speed-Shunde Cohort; **(B)** The NHANES.

**Abbreviations:** CKM, Cardiovascular-kidney-metabolic; CVD, cardiovascular disease; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; MASLD, Metabolic dysfunction-associated steatotic liver disease.

In the NHANES study, demographic data were obtained by self-reported variables, including age, gender, race/ethnicity, education level, smoking status, and alcohol consumption. NHANES provided detailed information describing the laboratory methodologies used to quantify numerous biomarkers, including plasma glucose levels, glycosylated hemoglobin, and lipid profiles. Data cleaning was conducted in accordance with the literature previously outlined.<sup>23</sup> The study categorized education levels into three groups: less than high school, high school, and beyond high school. Furthermore, the number of cigarettes smoked in a lifetime determined whether a person was a current smoker (lifetime  $\geq 100$  cigarettes and ongoing), a nonsmoker, or a former smoker (quit  $\geq 6$  months).<sup>24</sup>

## Definitions of MASLD and Fibrosis

In the Speed-Shunde cohort and the NHANES study, CAP and LSM were measured using VCTE with the FibroScan<sup>®</sup> 402 and 502 V2 Touch models, respectively. Prior to the examination, participants underwent a standardized fast of at least 3 hours. The procedure was conducted by trained technicians using VCTE, with the probe selection (medium (M) or extra-large (XL)) determined by the manufacturer's BMI-based guidance. Measurements were considered reliable only if they achieved an interquartile range-to-median (IQR/M) ratio of  $\leq 30\%$  and a success rate of at least 60%. Measurements with  $< 10$  valid shots or that did not meet reliability criteria were repeated or excluded. Participants underwent VCTE assessment to identify hepatic steatosis (CAP  $\geq 248$  dB/m)<sup>20</sup> and fibrosis (LSM  $\geq 7.0$  kPa).<sup>25</sup> The diagnosis of MASLD required hepatic steatosis meeting the criteria of at least one of five cardiometabolic risk factors.<sup>7</sup> Metabolic and alcohol-associated liver disease is defined as MASLD patients with high weekly alcohol intake (defined as 140–350 g for women and 210–420 g for men). Additionally, the history of other liver diseases includes hepatitis B or C, metabolic and alcohol-associated liver disease, alcohol-associated liver disease, and cryptogenic steatotic liver disease.

## Definition of CKM Syndrome

We defined CKM syndrome stages as adherence to the criteria outlined in the AHA Presidential Advisory Statement.<sup>1</sup> The estimated glomerular filtration rate (eGFR) was calculated using the 2021 race-free Chronic Kidney Disease Epidemiology Collaboration creatinine equation.<sup>26</sup> Albuminuria was defined as a urinary albumin-to-creatinine ratio (UACR)  $\geq 30$  mg/g. The stage of CKD was determined using the KDIGO criteria based on eGFR and UACR. Using the PREVENT equations,<sup>18</sup> a 10-year cardiovascular disease (CVD) risk  $\geq 20\%$  was considered high. Subclinical CVD was defined as having either a  $\geq 20\%$  10-year CVD risk or a high-risk of CKD. A comprehensive variable-definition map is provided in [Table S1](#). The stages are defined as follows: Stage 0 (characterized by the absence of CKM risk factors), Stage 1 (defined by the presence of excess or dysfunctional adiposity), Stage 2 (marked by the co-occurrence of metabolic risk factors and moderate to high-risk CKD), Stage 3 (where subclinical CVD manifests), and Stage 4 (which involves clinical CVD). Non-advanced CKM syndrome was considered present at stage  $\leq 2$ , and advanced CKM syndrome stages were characterized by stages 3 and 0.<sup>1,2</sup>

## Statistical Analysis

Appropriate statistical techniques were applied to respect the respective survey designs. In Speed-Shunde, we accounted for the multistage sampling using cluster-robust standard errors (SE) at the town level. The NHANES data were analyzed using the provided strata, primary sampling units (PSU), and examination weights (WTMEC2YR) as per the NCHS analytical guidelines. Baseline characteristics were summarized using frequencies and percentages (%) for categorical variables and means  $\pm$  standard deviation for continuous variables. Differences between groups were assessed using *t*-tests, chi-square tests, or Mann–Whitney *U*-tests as appropriate. Baseline characteristics of included subjects and those excluded due to missing data are presented in [Table S2](#). The patterns of co-existence and the frequency of overlapping combinations among CKM syndrome, MASLD, and hepatic fibrosis were quantified. A multivariable logistic regression model was applied in the Speed-Shunde cohort to evaluate odds ratios (ORs) and their 95% Confidence Intervals (CIs) for the relationship between CAP, LSM, MASLD, and MASLD-related fibrosis and the prevalence of advanced CKM syndrome. The comprehensive model in the Speed-Shunde Cohort was adjusted for age, sex, education, and smoking behavior. A survey-weighted multivariable logistic regression model in the NHANES study was employed to examine the associations between CAP, LSM, MASLD, and MASLD-related fibrosis and the prevalence of advanced CKM syndrome, with additional adjustment for race/ethnicity. All confounding variables exhibited variance inflation factors below 5, indicating no substantial multicollinearity. To assess the

dose-response relationship between advanced CKM syndrome and CAP or LSM, a restricted cubic spline (RCS) with three knots (at the 10th, 50th, and 90th percentiles) was used, setting the cohort median as the reference point. Data analysis was conducted using IBM SPSS Statistics (version 24) and R (version 4.2.2), with a two-sided P-value of <0.05 indicating statistical significance for all hypothesis tests.

## Results

### Baseline Characteristics

Table 1 presents the baseline characteristics of the study participants from the Speed-Shunde cohort and the NHANES. The Speed-Shunde cohort included 6186 participants (mean age 48.61±12.6 years; 38.8% male; mean BMI 23.76±3.38 kg/m<sup>2</sup>). The majority (85.8%) reported never smoking, while 3.5% were former smokers and 10.7% were current smokers. The proportions of participants in CKM syndrome stages 0, 1, 2, 3, and 4 were 14.1%, 19.3%, 57.7%, 6.5%, and 2.3%, respectively. Notably, advanced CKM syndrome was observed in 8.8% of participants. Among the cohort, MASLD had a prevalence of 39.4%, and liver fibrosis was detected in 15.6% of individuals.

**Table 1** Baseline Characteristics of Participants

Variable	Speed-Shunde	NHANES (Unweighted)	NHANES (Weighted)
<b>N</b>	6186	6072	170,414,047
<b>Age, years</b>	48.61±12.60	51.4±17.8	48.61±0.59
<b>BMI, kg/m<sup>2</sup></b>	23.76±3.38	29.0±7.0	28.73±0.19
<b>Men, %</b>	38.8	48.6	48.4
<b>Education, %</b>			
Less than high school	43.0	18.6	10.8
High school	23.6	23.3	25.8
Beyond high school	33.4	58.1	63.4
<b>Smoking status, %</b>			
No	85.8	61.6	61.3
Ever	3.5	22.3	24.3
Current	10.7	16.1	14.5
<b>Race/ethnicity, %</b>			
Mexican American	–	10.0	7.1
Non-Hispanic Asian	–	14.0	6.9
Non-Hispanic Black	–	27.8	12.0
Non-Hispanic White	–	33.8	63.1
Other Hispanic	–	9.8	7.3
Other Race	–	4.7	3.7
<b>CKM syndrome Stages, %</b>			
Stage 0	14.1	11.1	14.9
Stage 1	19.3	22.8	25.5
Stage 2	57.7	46.3	44.8
Stage 3	6.5	8.3	5.9
Stage 4	2.3	11.4	9.0
<b>Advanced CKM, %</b>	8.8	19.8	14.9
<b>CAP, dB/m</b>	240.87±50.92	253.00±63.00	250.56±1.72
<b>LSM, kPa</b>	5.60±1.90	5.89±5.03	5.71±0.12
<b>MASLD, %</b>	39.4	45.0	42.6
<b>Fibrosis, %</b>	15.6	15.5	14.5

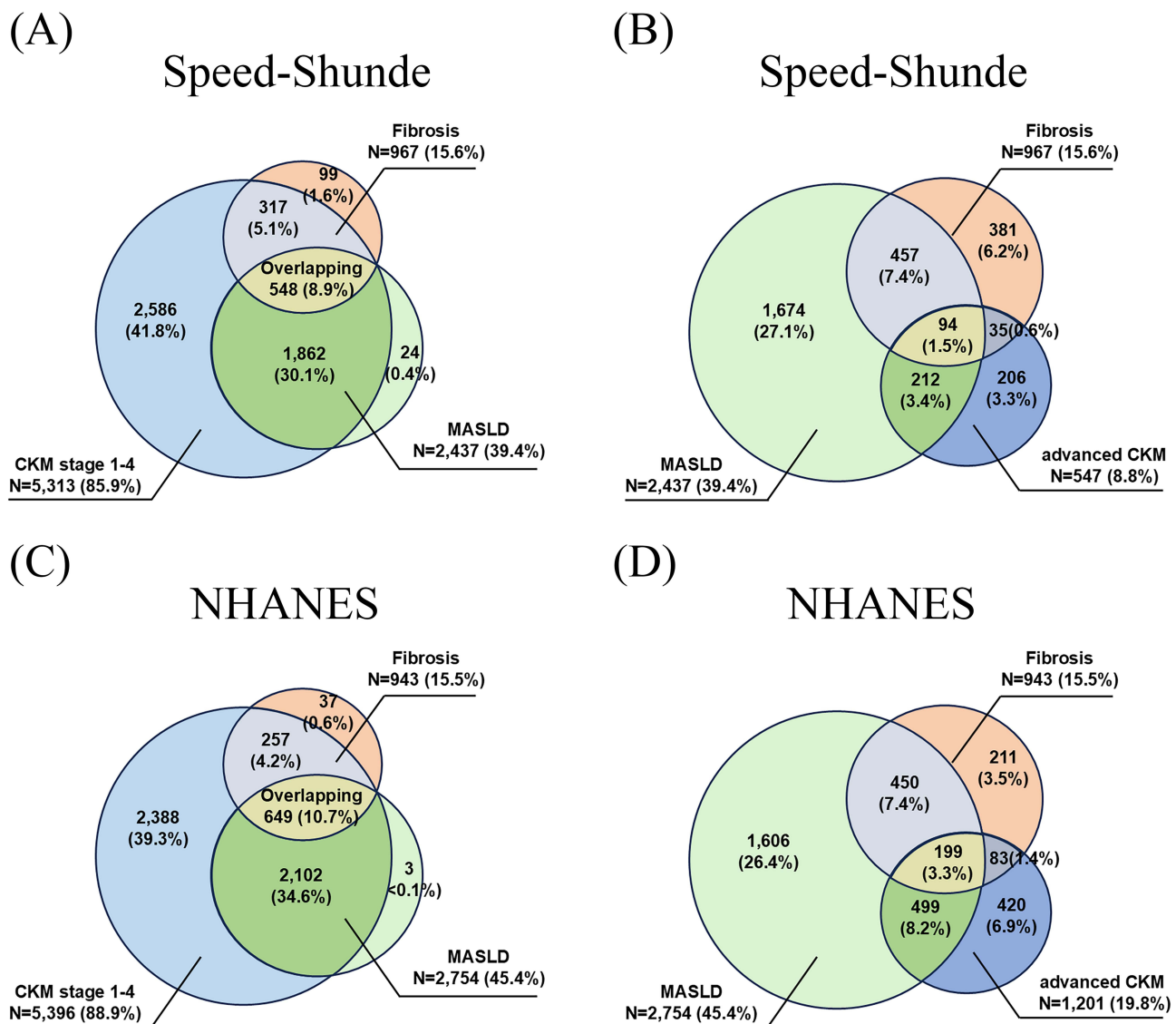
**Notes:** The baseline characteristics of participants were summarized using percentages (%) for categorical variables and mean ± standard for continuous variables. Appropriate survey weights were applied to all analyses of NHANES data.

**Abbreviations:** BMI, body mass index; CKM syndrome, Cardiovascular-kidney-metabolic syndrome; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; MASLD, metabolic dysfunction-associated steatotic liver disease.

The NHANES population sample, weighted to represent approximately 170 million United States adults (mean age  $48.61 \pm 0.59$  years; 48.4% male; mean BMI  $28.73 \pm 0.19$  kg/m<sup>2</sup>). Regarding smoking habits, the majority of participants (61.3%) reported never having smoked, while 24.3% were former smokers and 14.5% were current smokers. The racial/ethnic composition included 7.1% Mexican American, 6.9% non-Hispanic Asian, 12.0% non-Hispanic Black, 63.1% non-Hispanic White, 7.3% other Hispanic, and 3.7% other race. The proportions of participants with CKM syndrome stages 0, 1, 2, 3, and 4 were 14.9%, 25.5%, 44.8%, 5.9%, and 9.0%, respectively, while advanced CKM syndrome was observed in 14.9% of participants. Among the NHANES, MASLD had a prevalence of 42.6%, and liver fibrosis was detected in 14.5% of individuals.

### The Overlaps Between CKM Syndrome, MASLD, and Fibrosis

Figure 2 depicts a Venn diagram showing the frequencies and overlaps of CKM syndrome, MASLD, and fibrosis. In the Speed-Shunde cohort of 6186 participants, 98.9% of individuals with MASLD met criteria for CKM stages 1–4, compared with 89.5% of individuals with fibrosis. There were 1862 participants of overlap between MASLD and



**Figure 2** Venn diagram indicating the frequency and overlap of CKM syndrome, MASLD, and fibrosis. **(A)** Overlap of CKM stages 1–4, MASLD, and fibrosis in the Speed-Shunde Cohort; **(B)** Overlap of advanced CKM, MASLD, and fibrosis in the Speed-Shunde Cohort; **(C)** Overlap of CKM stages 1–4, MASLD, and fibrosis in the NHANES study; **(D)** Overlap of advanced CKM, MASLD, and fibrosis in the NHANES study; Numbers and proportions of the population within each overlapping segment are provided.

**Abbreviations:** CKM, Cardiovascular-kidney-metabolic; MASLD, Metabolic dysfunction-associated steatotic liver disease.

CKM stages 1–4, 317 participants of overlap between fibrosis and CKM stages 1–4, and 548 overlaps across all three categories (Figure 2A). Furthermore, overlaps were observed in 457 with both MASLD and fibrosis, 212 with MASLD and advanced CKM, 35 with fibrosis and advanced CKM, and 94 with all three conditions (Figure 2B).

In the NHANES population sample of 6,72 persons in the United States, 99.9% of participants met the criteria for CKM stages 1–4, whereas 96.1% of individuals with fibrosis also met these criteria. There were 2102 cases of overlap between MASLD and CKM stages 1–4, 257 cases of overlap between fibrosis and CKM stages 1–4, and 649 cases involving all three conditions (Figure 2C). Further overlap analyses demonstrated that 450 had both MASLD and fibrosis, 499 had MASLD and advanced CKM, 83 had fibrosis and advanced CKM, and 199 presented with all three conditions concurrently (Figure 2D).

## Prevalence of Overlapping CKM Syndrome Stages in Participants with MASLD and MASLD-Related Fibrosis

Table 2 illustrates the prevalence of overlapping CKM syndrome stages among individuals with MASLD. In the Speed-Shunde cohort, the distribution of CKM syndrome stages differed significantly between participants without MASLD ( $n = 3749$ ) and those with MASLD ( $n = 2437$ ) ( $P < 0.001$ ). In the non-MASLD group, 22.6%, 23.2%, 47.9%, 4.3%, and 2.1% were classified as stages 0–4, respectively. In contrast, in the MASLD group, the proportions were 1.1%, 13.4%, 73.0%, 10.0%, and 2.6%, respectively. In addition, the prevalence of advanced CKM syndrome (stages 3–4) was higher in the MASLD group compared with the non-MASLD group (12.6% vs 6.4%,  $P < 0.001$ ). Similarly, in the NHANES population, the stage distribution also showed significant differences ( $P < 0.001$ ). In the non-MASLD group, 25.8%, 28.4%, 35.8%, 3.9%, and 6.0% were classified as stages 0–4, respectively, compared with 0.1%, 21.5%, 56.8%, 8.5%, and 13.1% in the MASLD group. Furthermore, the prevalence of advanced CKM syndrome was higher in the MASLD group compared with the non-MASLD group (21.5% vs 9.9%,  $P < 0.001$ ).

Table 3 illustrates the prevalence of overlapping CKM syndrome stages among individuals with MASLD-related fibrosis. The distribution of CKM syndrome stages in the Speed-Shunde cohort exhibited a significant difference between MASLD individuals without fibrosis ( $n = 1886$ ) and those with fibrosis ( $n = 551$ ) ( $P < 0.001$ ). In the non-fibrosis group, the distribution across stages 0–4 was 1.3%, 14.8%, 72.6%, 9.1%, and 2.1%, respectively. In the MASLD-related fibrosis group, the proportions for stages 0 to 4 were 0.5%, 8.3%, 74.0%, 12.9%, and 4.2%, respectively. The prevalence of advanced CKM syndrome (stages 3–4) was greater in the MASLD-related fibrosis group compared to the non-fibrosis group (17.1% vs 11.2%,  $P < 0.001$ ). In the NHANES population, the distribution of CKM stages exhibited substantial variations ( $P < 0.001$ ). In the non-fibrosis group, the percentages classified as stages 0–4 were 0.1%, 23.9%, 55.8%, 8.2%, and 12.0%, respectively. In the MASLD-related fibrosis group, the percentages were 0%, 9.7%, 62.0%, 10.0%, and

**Table 2** Prevalence of Overlapping CKM Syndrome Stages in Participants with MASLD

Variable	Speed-Shunde			NHANES (Weighted)		
	Non-MASLD	MASLD	P value <sup>a</sup>	Non-MASLD	MASLD	P value <sup>a</sup>
<b>N</b>	3749	2437		97,864,267	72,549,781	
<b>CKM syndrome Stages, % (95%CI)</b>			<0.001**			<0.001**
Stage 0	22.6(21.2,23.9)	1.1(0.7,1.6)		25.8(22.6,29.1)	0.1 (-0.1, 0.3)	
Stage 1	23.2(21.8,24.5)	13.4(12.0,14.8)		28.4(26.0,30.9)	21.5(18.7,24.4)	
Stage 2	47.9(46.2,49.5)	73.0(71.1,74.7)		35.8(32.3,39.4)	56.8 (52.6,61.2)	
Stage 3	4.3(3.7,5.0)	10.0(8.8,11.2)		3.9(2.9,4.9)	8.5 (7.2,9.8)	
Stage 4	2.1(1.7,2.6)	2.6(2.0,3.3)		6.0(4.9, 7.2)	13.1(10.7,15.4)	
<b>Advanced CKM, % (95%CI)</b>	6.4(5.7,7.3)	12.6(11.3,13.9)	<0.001**	9.9(8.3,11.6)	21.5(18.9,24.2)	<0.001**
<b>Fibrosis, % (95%CI)</b>	11.1(10.1,12.1)	22.6(21.0,24.3)	<0.001**	7.7(6.1,9.24)	23.7(21.2,26.1)	<0.001**

**Notes:** The baseline characteristics of participants were summarized using percentages (%) and 95% CIs for categorical variables and mean  $\pm$  standard for continuous variables; <sup>a</sup>Indicates difference between two groups with the t-tests, chi-square tests, or Mann–Whitney U-tests as appropriate; Appropriate survey weights were applied to all analyses of NHANES data; \*\*  $P < 0.01$ .

**Abbreviations:** CKM syndrome, Cardiovascular-kidney-metabolic syndrome; MASLD, metabolic dysfunction–associated steatotic liver disease.

**Table 3** Prevalence of Overlapping CKM Syndrome Stages in Participants with MASLD-Related Fibrosis

Variable	Speed-Shunde			NHANES (Weighted)		
	Non-Fibrosis	Fibrosis	P value <sup>a</sup>	Non-Fibrosis	Fibrosis	P value <sup>a</sup>
<b>N</b>	1886	551		55,385,186	17,164,595	
<b>CKM syndrome Stages, % (95%CI)</b>			<0.001**			<0.001**
Stage 0	1.3(0.8,1.9)	0.5(0.1,1.6)		0.1 (-0.1,0.3)	0.0(0.0,0.0)	
Stage 1	14.8(13.3,16.5)	8.3(6.2,11.0)		23.9(20.5,27.3)	9.7(6.8,12.5)	
Stage 2	72.6(70.6,74.6)	74.0(70.2,77.7)		55.8(51.2,60.4)	62.0(56.5,67.4)	
Stage 3	9.1(7.9,10.5)	12.9(10.2,16.0)		8.2(6.5, 9.8)	10.0(6.3,13.8)	
Stage 4	2.1(1.5,2.9)	4.2(2.7,6.2)		12.0(9.5,14.5)	18.4(14.8,22.0)	
<b>Advanced CKM, % (95%CI)</b>	11.2(9.8,12.8)	17.1(14.0,20.5)	<0.001**	20.1(17.6,22.7)	28.4(22.7,34.1)	0.002**

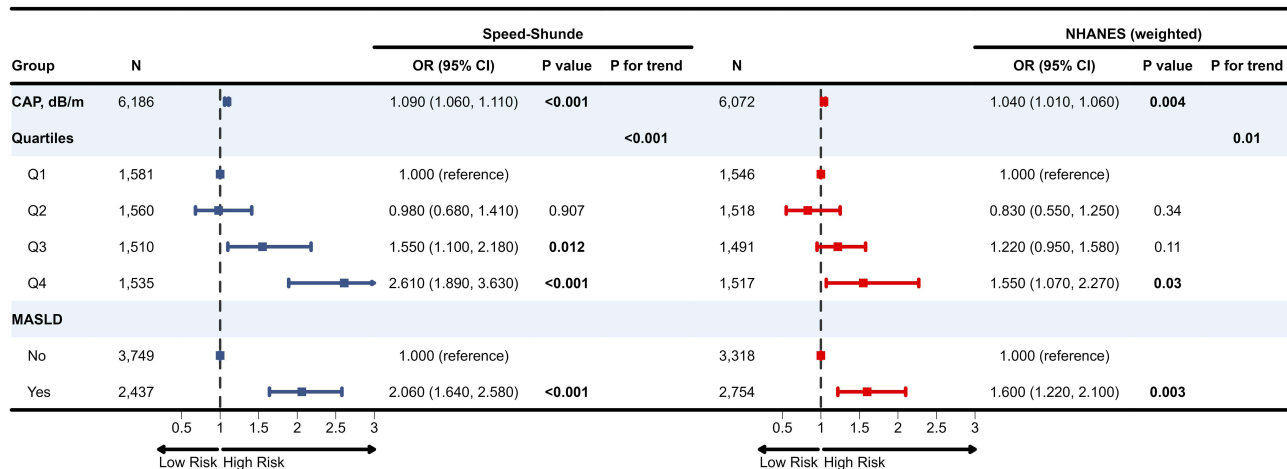
**Notes:** The baseline characteristics of participants were summarized using percentages (%) and 95% CIs for categorical variables and mean ± standard for continuous variables; <sup>a</sup>Indicates difference between two groups with the *t*-tests, chi-square tests, or Mann–Whitney *U*-tests as appropriate; Appropriate survey weights were applied to all analyses of NHANES data; \*\* *P*<0.01.

**Abbreviations:** CKM syndrome, Cardiovascular-kidney-metabolic syndrome; MASLD, metabolic dysfunction–associated steatotic liver disease.

18.4%, respectively. The prevalence of advanced CKM syndrome was again higher in the MASLD-related fibrosis group than in the non-fibrosis group (28.4% vs 20.1%, *P* = 0.002). Table S3 presents the unweighted prevalence of overlapping CKM syndrome stages with MASLD and MASLD-related fibrosis among NHANES participants.

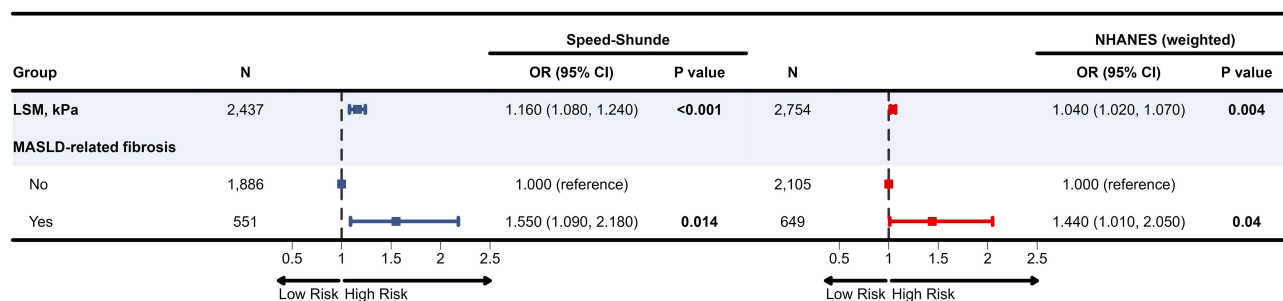
### Associations of CAP and MASLD with Advanced CKM Syndrome

Figure 3 depicts the results of a multivariable logistic regression analysis of the association between CAP and MASLD with advanced CKM syndrome. CAP was evaluated as a continuous and a categorical variable, based on quartiles in the general population. Each 10-unit increase in CAP values was positively associated with the prevalence of advanced CKM syndrome in both the Chinese (OR: 1.09, 95% CI: 1.06, 1.11) and the United States (OR: 1.04, 95% CI: 1.01, 1.06) populations. Compared to the lowest quartile (Q1), in the highest quartile of CAP (Q4) was associated with an increased odds of advanced CKM syndrome in both the Chinese (OR:2.61, 95% CI:1.89,3.63) and United States (OR:1.55, 95% CI: 1.07, 2.27) populations, with a significant linear trend across quartiles (*P* for trend < 0.001 for both). Compared with non-MASLD individuals, MASLD was independently associated with increased odds of advanced CKM stages, with ORs of 2.06 (95% CI: 1.64, 2.58) in the Chinese and 1.60 (95% CI: 1.22, 2.10) in the United States (both *P* < 0.01).



**Figure 3** CAP and MASLD associations with advanced CKM syndrome, as assessed by multivariable logistic regression models. CAP values (dB/m) in the Speed-Shunde Cohort were categorized into quartiles: Q1 (100–205), Q2 (205–235), Q3 (235–270), and Q4 (270–400). CAP values (dB/m) in the NHANES study were categorized into quartiles: Q1 (100–209), Q2 (209–243), Q3 (243–296), and Q4 (296–400). The associations between advanced CKM syndrome and MASLD or CAP in the total population were analyzed using multivariable logistic regression models. The comprehensive model in the Speed-Shunde Cohort was controlled for age, sex, education, and smoking status, while in the NHANES study, it was further adjusted for race/ethnicity. Bold font indicates statistically significant differences (*P*<0.05).

**Abbreviations:** OR, odds ratio; CI, confidence interval; CKM, Cardiovascular-kidney-metabolic; CAP, controlled attenuation parameter; MASLD, Metabolic dysfunction-associated steatotic liver disease.



**Figure 4** LSM and MASLD-related fibrosis associations with advanced CKM syndrome, as assessed by multivariable logistic regression models. The associations between advanced CKM syndrome and MASLD-related fibrosis or LSM among individuals with MASLD were analyzed using multivariable logistic regression models. The comprehensive model in the Speed-Shunde Cohort was controlled for age, sex, education, and smoking status, while in the NHANES study, it was further adjusted for race/ethnicity. Bold font indicates statistically significant differences ( $P < 0.05$ ).

**Abbreviations:** OR, odds ratio; CI, confidence interval; CKM, Cardiovascular-kidney-metabolic; LSM, liver stiffness measurement; MASLD, Metabolic dysfunction-associated steatotic liver disease.

## Associations of LSM and MASLD-Related Fibrosis with Advanced CKM Syndrome

Figure 4 depicts the results of a multivariable logistic regression analysis of the association between LSM and MASLD-related fibrosis with advanced CKM syndrome. Higher LSM values were positively associated with the prevalence of advanced CKM syndrome in both Chinese (OR: 1.16, 95% CI: 1.08, 1.24) and United States (OR: 1.04, 95% CI: 1.02, 1.07) MASLD participants. Moreover, MASLD participants with fibrosis were associated with higher odds of advanced CKM syndrome stages compared to those without fibrosis, with ORs of 1.55 (95% CI: 1.09, 2.18) in the Speed-Shunde cohort and 1.44 (95% CI: 1.01, 2.05) in the NHANES.

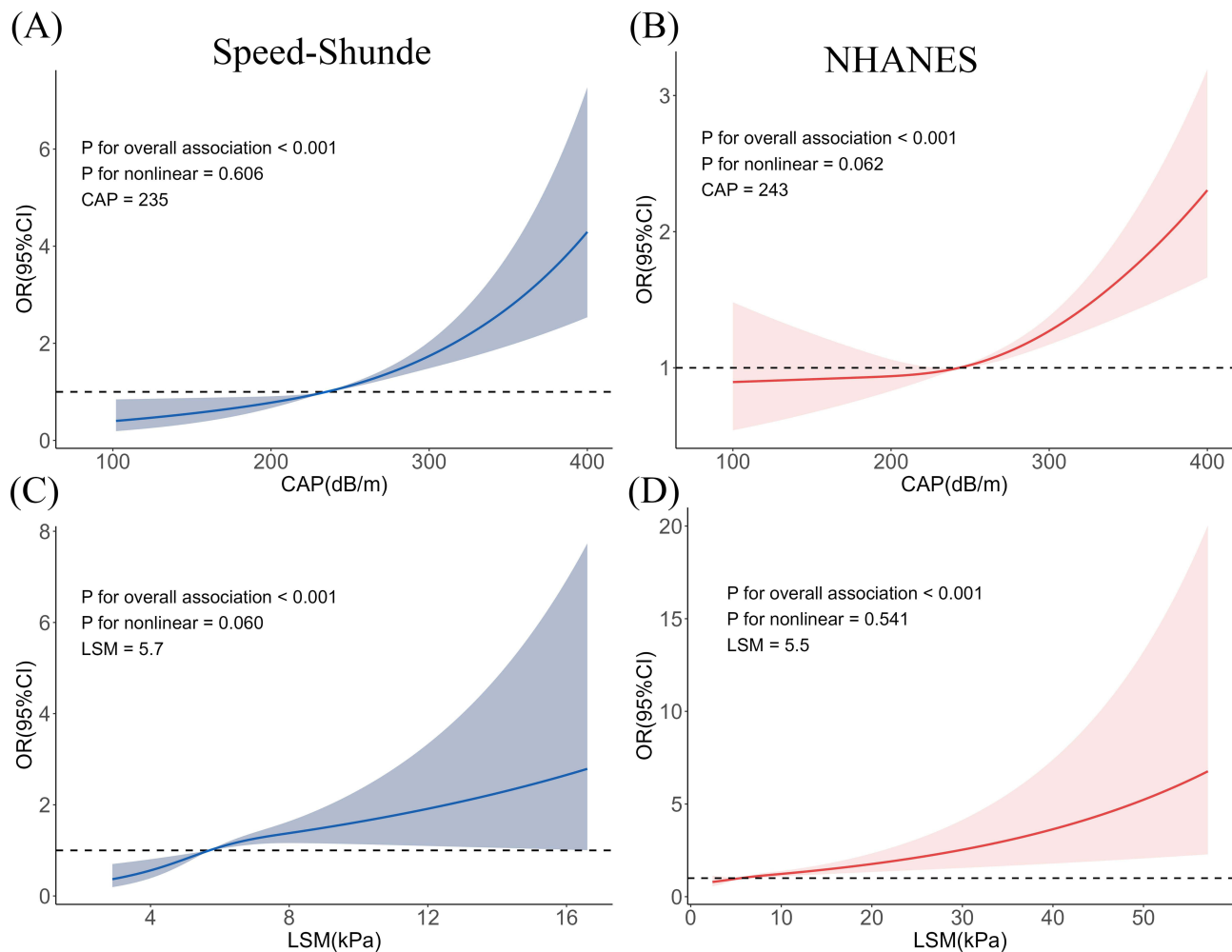
## Non-Linear Relationships Among CAP, LSM, and Advanced CKM Syndrome

Figure 5 demonstrates the dose-response correlation between advanced CKM syndrome and CAP in the general population, as well as between advanced CKM and LSM in individuals with MASLD. RCS analyses showed a positive linear relationship of CAP values with advanced CKM syndrome in both the Chinese and United States populations ( $P$  non-linear  $> 0.05$  and  $P$  overall  $< 0.05$ ). The OR crossed 1.0 at CAP values of approximately 235 dB/m in China and 243 dB/m in the United States, as shown in the spline curves (Figure 5A and B). Similarly, RCS analyses revealed a positive linear relationship between LSM values and advanced CKM syndrome in both Chinese and United States MASLD participants ( $P$  non-linear  $> 0.05$  and  $P$  overall  $< 0.05$ ). Furthermore, the OR crossed 1.0 at LSM values of approximately 5.7 kPa in China and 5.5 kPa in the United States, as shown in the spline curves (Figure 5C and D).

## Discussion

To our knowledge, this work is an initial effort to investigate the associations of MASLD and its related fibrosis (via VCTE-based CAP/LSM) with the likelihood of having advanced CKM syndrome (stages 3–4) in a large, community-based Chinese population, with findings externally validated in the US NHANES cohort. Our primary findings are as follows: First, higher CAP values and MASLD were significantly correlated with elevated odds of advanced CKM syndrome. Second, higher LSM values and MASLD-related fibrosis were significantly associated with a higher likelihood of being in advanced CKM syndrome compared to individuals without fibrosis. Third, both CAP and LSM values exhibited positive, linear relationships with advanced CKM syndrome. Notably, these robust associations were consistent in both the Chinese and US populations, which vary in ethnicity and lifestyle. These findings support the importance of evaluating liver health, particularly MASLD and associated fibrosis (eg, via VCTE-based CAP/LSM), for risk stratification in CKM syndrome.

Considering the common risk factors, overlapping physiological mechanisms, and management strategies in both MASLD and CKM frameworks,<sup>16,27</sup> there is an appeal to graft the two together. In this study, we quantified the prevalence of MASLD and associated fibrosis across the CKM syndrome spectrum and characterized their overlap and correlations in Chinese and US populations. Approximately 90% of patients were classified in CKM stages 1–4, with high prevalences of MASLD (39.4%



**Figure 5** Non-linear associations among CAP, LSM, and advanced CKM syndrome. **(A)** Non-linear associations between CAP and advanced CKM in the Speed-Shunde Cohort; **(B)** Non-linear associations between CAP and advanced CKM in the NHANES study; **(C)** Non-linear associations between LSM and advanced CKM in the Speed-Shunde Cohort; **(D)** Non-linear associations between LSM and advanced CKM in the NHANES study; Non-linear associations between advanced CKM and CAP in the general population, as well as between advanced CKM and LSM in individuals with MASLD. An analysis employing RCS was conducted. The comprehensive model in the Speed-Shunde Cohort was controlled for age, sex, education, and smoking status, while in the NHANES study, it was further adjusted for race/ethnicity. The solid lines and shaded areas represent the central risk estimates and 95% CIs.

**Abbreviations:** RCS, restricted cubic splines; CKM, Cardiovascular-kidney-metabolic; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; MASLD, Metabolic dysfunction-associated steatotic liver disease.

in China; 42.6% in the US) and liver fibrosis (15.6% in China; 14.5% in the US), consistent with the global epidemiology of these diseases.<sup>3,6,7,28</sup> Notably, there was substantial overlap among MASLD, fibrosis, and the stages of CKM syndrome, with nearly all individuals with MASLD and the majority with fibrosis presenting with CKM syndrome stages 1–4. The significant overlap is partially due to a definitional tautology, as CKM stage  $\geq 1$  embeds metabolic criteria that overlap with MASLD definitions,<sup>1,7</sup> the near-universal co-occurrence should not be over-interpreted. Advanced CKM syndrome (Stages 3–4)—a high-risk condition characterized by a significantly increased burden of overt clinical disease and a worse prognosis—was present in 8.8% of the Chinese and 14.9% of the US populations. The study further identified a subset of individuals with co-occurring MASLD and/or fibrosis and advanced CKM syndrome. Given this context, we therefore focused on characterizing the relationships between MASLD, its associated fibrosis, and advanced CKM syndrome.

MASLD is increasingly acknowledged as a pivotal contributor to development and progression of subclinical ASCVD,<sup>12,29–31</sup> clinical CVD,<sup>13,32,33</sup> and CKD.<sup>14,15</sup> A cohort study encompassing 26,676 patients with steatotic liver disease demonstrated that MASLD exhibited a 2.52-fold elevated risk of heart failure.<sup>34</sup> Furthermore, a meta-analysis of sixteen retrospective cohort studies identified a significant connection between MASLD and an increased long-term risk of

developing atrial fibrillation.<sup>35</sup> It is also well-documented that MASLD significantly increases the risk of both incident CKD and abnormal proteinuria.<sup>14,36,37</sup> However, previous research has primarily examined the link between hepatic steatosis (or MASLD) and single-organ diseases (eg, type 2 diabetes, CKD, or CVD). There is still a significant knowledge gap concerning how MASLD and CKM syndrome are interconnected as part of a unified, progressive continuum. In the present study, the prevalence of advanced CKM syndrome was significantly higher in the MASLD group compared to the non-MASLD group. Correspondingly, MASLD and higher CAP values were significantly associated with elevated odds of advanced CKM syndrome (stages 3–4). More recently, a cross-sectional study by Yang et al<sup>38</sup> found that the hepatic steatosis (assessed by the Framingham Steatosis Index, FSI) was significantly associated with an increased risk of advanced CKM syndrome. Similarly, a retrospective Korean cohort study by Kim et al<sup>39</sup> reported that hepatic steatosis (defined by a fatty liver index (FLI)  $\geq 60$ ) was also associated with a higher risk of cardiovascular events across the spectrum of CKM stages. Liu et al<sup>40</sup> identified non-alcoholic fatty liver disease (NAFLD) as a key driver accelerating CKM progression and mortality. In contrast to above studies that relied on surrogate markers for hepatic steatosis (eg, FSI/FLI) and did not evaluate the new MASLD definition, our study employed VCTE-based CAP as a non-invasive method to diagnose and quantify MASLD, providing more direct evidence for its independent association with advanced CKM syndrome.

It is also increasingly recognized that the presence and severity of liver fibrosis in MASLD are independently associated with both cardiovascular and renal outcomes. Studies using non-invasive fibrosis assessment tools, such as the Fibrosis-4 (FIB-4) Index, NAFLD Fibrosis Score (NFS), and VCTE, indicate that higher fibrosis scores are linked to a greater risk of major adverse cardiovascular events, CKD, and mortality.<sup>41–43</sup> In addition, the AHA scientific statement on CKM syndrome endorses screening for advanced liver fibrosis using the FIB-4 index every 1–2 years in patients with MASLD who have coexisting metabolic risk factors (typically CKM stage 2 or higher).<sup>1</sup> However, whether the presence and severity of liver fibrosis (VCTE-based LSM) in MASLD confer a risk of advanced CKM syndrome remains unclear. In the present study, we observed that elevated LSM values and MASLD-related fibrosis were significantly associated with a higher risk of advanced CKM syndrome. This finding is consistent with earlier studies that employed non-invasive liver fibrosis scores like FIB-4 and NFS. Liu et al<sup>40</sup> showed that the prevalence of advanced liver fibrosis (defined by FIB-4) increased markedly in individuals at higher CKM stages. Additionally, research by Ren et al<sup>44</sup> demonstrated that the relationship between liver fibrosis, as measured by NFS, and increased cardiorenal disease risk, as well as CKM stage, exists independently of traditional risk factors in diabetic patients. In a cohort of individuals with similar CKM stages, those with advanced liver fibrosis were significantly associated with higher all-cause mortality.<sup>40</sup> Collectively, the existing literature indicates that the extent of liver fibrosis is an important modifier of the global risk profile among individuals with CKM. Notably, the presence of MASH and liver fibrosis thus provides extra rationale for the lifestyle and pharmacologic interventions (eg, incretin therapies) already recommended for CVD prevention in patients with CKM syndrome.<sup>2</sup> Therefore, our findings provide insight that individuals diagnosed with MASLD, particularly those with advanced liver fibrosis identified by LSM, should be regarded as high-risk populations (CKM stages 3 to 4).

The strong correlation between MASLD, MASLD-related fibrosis, and advanced CKM syndrome could be mechanistically plausible. The liver's central role in metabolic homeostasis means that hepatic steatosis initiates a cascade of systemic disturbances.<sup>45</sup> The lipotoxic environment exacerbates oxidative stress,<sup>46</sup> activating inflammatory pathways (eg, NF- $\kappa$ B) and prompting the steatotic liver to secrete pro-inflammatory cytokines (eg, TNF- $\alpha$ , IL-6)<sup>47</sup> and pro-thrombotic factors (eg, PAI-1).<sup>48</sup> These mediators induce systemic inflammation, endothelial dysfunction, and hepatic and peripheral insulin resistance, which are essential contributors to the progression of ASCVD and CKD.<sup>49</sup> The progression to liver fibrosis signifies a significant intensification, significantly worsening this systemic metabolic and inflammatory dysregulation.<sup>50</sup> The fibrotic process extends beyond hepatic scarring; it enhances the secretion of profibrotic and inflammatory mediators that can cause direct or indirect harm to extrahepatic tissues. This multifactorial injury to the vascular endothelium and renal glomeruli provides a mechanistic basis for the progression of CKM syndrome to its advanced stages,<sup>51</sup> thereby contributing to an increased risk of advanced CKM syndrome. Nonetheless, higher CKM stages may also accelerate MASLD progression. Thus, whether the relationship between MASLD, MASLD-related fibrosis, and advanced CKM syndrome is causal or primarily driven by shared metabolic risk factors remains uncertain. Further longitudinal studies and mechanistic investigations are warranted.

Interestingly, CAP values in the general population and LSM values among individuals with MASLD both showed linear positive associations with advanced CKM risk. Our earlier work demonstrated independent associations of CAP and LSM

with 10-year ASCVD risk in the general population, with CAP  $\geq 301$  dB/m marking a sharp rise in ASCVD risk,<sup>52</sup> providing a potential threshold for family physicians to intensify cardiovascular risk stratification. In addition, findings from a cross-sectional study by Zhang et al<sup>53</sup> indicated that LSM is linearly and positively associated with carotid atherosclerosis and brachial-ankle pulse wave velocity, suggesting that LSM may serve as a useful predictor of subclinical atherosclerosis in patients with MASLD. Notably, we observed that the OR crossed 1.0 at CAP values of 235–243 dB/m and LSM values of 5.5–5.7 kPa—thresholds that lie near, or even slightly below, commonly accepted cut-offs for hepatic steatosis and clinically significant fibrosis.<sup>20</sup> Together, these findings support the potential utility of VCTE as quantitative imaging biomarkers for CKM risk stratification. CAP and LSM, employed for early MASLD detection and liver fibrosis assessment within the CKM framework, can effectively identify high-risk populations (CKM stages 3 to 4). Moreover, future research should evaluate whether incorporating VCTE parameters, such as CAP and LSM, into CKM staging and established prediction models, such as the PREVENT equations, provides incremental prognostic value.

The study's strengths include the use of a large, community-based Chinese cohort and external validation with US NHANES data. Despite the US population having a higher average BMI and greater prevalence of advanced CKM syndrome (14.9% vs 8.8%), the associations of MASLD and liver fibrosis with advanced CKM were consistent across both populations. This cross-validation improves the data's generalizability and reliability. The study also used objective, quantitative, non-invasive tools, such as VCTE, to assess hepatic steatosis and fibrosis, addressing the limitations of conventional biochemical scores and ultrasonography. Despite its strengths, this study has limitations. First, both the Speed-Shunde and NHANES investigations are cross-sectional. Since the data only show prevalence and associations at a single point, it is not possible to draw direct conclusions about causality. The critical question of whether MASLD directly drives the progression of CKM syndrome or, conversely, if severe CKM syndrome promotes the development of MASLD and hepatic fibrosis, remains unanswered. Furthermore, the possibility that a common underlying pathophysiological factor drives both conditions warrants careful consideration. We need longitudinal studies to understand the sequence of events and causal pathways linking the progression of MASLD, the development of fibrosis, and the progression of CKM syndrome. Second, the presence of missing data represents a limitation, potentially introducing bias to our estimates and reducing the generalizability of the results. Third, only clinical characteristics present in the Speed-Shunde and NHANES cohorts were considered in the analysis. The absence of data on subclinical heart failure, peripheral arterial disease, subclinical ASCVD, and atrial fibrillation in both datasets may have resulted in underestimation of CKM stages 3 and 4. The observed comorbidity between MASLD and CKM syndrome in this study is based solely on the Speed-Shunde (China) and NHANES (United States) cohorts. While the findings are context-specific to these populations, it is crucial to acknowledge that the Speed-Shunde cohort used robust sampling techniques, thereby improving its generalizability to the broader Chinese population.

## Conclusion

In conclusion, within a community-based Chinese cohort, validated in the United States NHANES, both MASLD and MASLD-related fibrosis were associated with a higher prevalence of advanced CKM syndrome (stages 3–4), and higher CAP/LSM levels showed positive linear associations with advanced CKM syndrome. Collectively, these findings support evaluating liver health (eg, VCTE-based CAP/LSM) when risk-stratifying CKM, while recognizing the cross-sectional design and measurement constraints. Prospective, mediation-aware, and mechanistic studies are needed to establish temporality, incremental prognostic value, and clinical utility.

## Abbreviations

AHA, the American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAP, controlled attenuation parameter; CARDIAL-MS, Cardio-Renal-DIAbetes-Liver-Metabolic Syndrome; CI, Confidence Intervals; CKM, Cardiovascular-kidney-metabolic syndrome; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; FIB-4, Fibrosis-4 Index; FLI, fatty liver index; FSI, Framingham Steatosis Index; IL-6, interleukin-6; KDIGO, Kidney Disease, Improving Global Outcomes; LSM, liver stiffness measurement; MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; NAFLD, non-alcoholic fatty liver disease; NCHS, National Center for Health Statistics; NF- $\kappa$ B, nuclear factor kappa-light-chain-enhancer of activated B cells; NFS, NAFLD Fibrosis Score; NHANES, National Health

and Nutrition Examination Survey; OR, odds ratios; PAI-1, plasminogen activator inhibitor-1; PSU, primary sampling units; RCS, restricted cubic spline; SE, standard errors; SPSS, Statistical Package for the Social Sciences; TNF- $\alpha$ , tumor necrosis factor-alpha; UACR, urinary albumin-to-creatinine ratio; VCTE, Vibration-controlled transient elastography.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Ethics Approval and Informed Consent

The study protocol of the Speed-Shunde study (20211103) was approved by the Ethics Committee of the Eighth Affiliated Hospital (The First People's Hospital of Shunde) of Southern Medical University in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed and written consent was obtained from all participants before enrollment. Trial registration: Registry: <http://www.chictr.org.cn/>, TRN: ChiCTR2100054130, Registration date: 9 December, 2021. Moreover, the NHANES data are publicly available and fully de-identified. The NHANES study protocol was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and all participants provided written informed consent. The NHANES procedures complied with the Declaration of Helsinki. Further details are available at <https://www.cdc.gov/nchs/nhanes/>. In accordance with Item 1 and Item 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (February 18, 2023, China), and as confirmed by the Ethics Committee, this study is exempt from additional ethical approval.

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 Lan Liu: Conceptualization, Resources, Supervision, Writing - Review & Editing;  
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 Jie Shen: Conceptualization, Funding Acquisition, Resources, Supervision, Writing - Review & Editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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