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Association of Cardiovascular-Kidney-Metabolic Syndrome with Kidney Stones: A Population-based Study

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Abstract

Background: The prevalence of kidney stones (KS) has been increasing globally, and their association with cardiovascular disease and metabolic syndrome suggests a shared underlying pathophysiology. However, the impact of different stages of cardiovascular-kidney-metabolic (CKM) syndrome on KS prevalence remains unclear.

Objective: This study aimed to investigate the association between the stages of cardiovascular-kidney-metabolic (CKM) syndrome and the prevalence of kidney stones (KS) in a nationally representative sample of adults in the United States.

Methods: A total of 15,568 participants aged ≥20 years were included in the National Health and Nutrition Examination Survey 2007–2020 fasting subsample. CKM syndrome stages (0–4) were defined based on the 2023 American Heart Association Presidential Advisory on CKM Health. The KS history was determined using self-reported data. Multivariable logistic regression models were used to assess the association between the CKM syndrome stage and KS prevalence.

Results: Of the 15,568 participants, 1,501 (9.64%) reported a history of KS. The KS prevalence increased progressively with advancing CKM stage, rising from 5.10% in stage 0 to 16.55% in stage 4 ($P < 0.001$). In the fully adjusted model, the odds ratios (ORs) for KS were 1.18 (95% confidence interval [CI]: 0.83–1.68) for Stage 1, 1.72 (95% CI: 1.28–2.32) for Stage 2, 2.00 (95% CI: 1.29–3.10) for Stage 3, and 2.36 (95% CI: 1.64–3.40) for Stage 4, compared to Stage 0 (P for trend < 0.001). Stratified analyses revealed no significant interactions between age, sex, race/ethnicity, or other subgroups.

Conclusion: This study demonstrated a significant stepwise increase in KS prevalence with the advancing stages of CKM syndrome. These findings highlight the importance of monitoring and managing CKM syndromes to mitigate the risks of KS.

Keywords: cardiovascular disease; kidney disease; metabolic syndrome; kidney stones; National Health and Nutrition Examination Survey.

Strengths of the Study:

Novel Approach: This is the first study to explore CKM syndrome stages in relation to kidney stones, offering new insights for future research.

Large Sample Size: This study utilized a large, nationally representative sample from NHANES, enhancing generalizability.

Limitations of the Study:

Cross-Sectional Design: The cross-sectional design prevents inference of causality between CKM syndrome and kidney stone development.

Limited Generalizability: The study included only U.S. adults, limiting the applicability of results to other populations or regions.

Introduction

Kidney stones (KS) are hard mineral deposits forming in the renal calyces and pelvis when urine concentrations of substances like calcium, oxalate, uric acid, or phosphate become high enough to crystallize[1]. KS affects 10.1% of the U.S. population[2]. Recent research suggests KS is a systemic disorder linked to chronic diseases such as cardiovascular diseases (CVD), diabetes, and obesity, rather than being limited to the kidneys. Stone formation is a complex process influenced by genetic, metabolic, and environmental factors[3].

The American Heart Association (AHA) recently defined the interconnectedness of obesity, type 2 diabetes mellitus (DM), CVD, chronic kidney disease (CKD), and other metabolic disorders[4]. These conditions share common risk factors like hypertension, insulin resistance, dyslipidemia, and systemic inflammation; progression of one often worsens others, creating a vicious cycle. CVD remains the leading cause of death in the U.S., while CKD and diabetes prevalence and mortality rates are rising[5, 6]. As these diseases increase, the prevalence of cardiovascular-kidney-metabolic (CKM) syndrome is expected to grow.

CKM syndrome comprises interconnected risk factors that elevate the likelihood of developing CVD, type 2 diabetes, and other health complications. Metabolic diseases such as obesity, diabetes mellitus (DM), and hypertension are associated with an increased risk of KS[7]. An 8-year follow-up study found a correlation between high blood pressure and KS development, with the risk further heightened when hypertension coexists with overweight conditions[8]. These factors can alter urine composition, metabolic processes, and kidney function, promoting stone formation. Specifically, increased acid excretion, low citrate levels, and high calcium excretion create a conducive environment for KS[9].

Emerging evidence supports the association between KS and various metabolic risk factors. Unhealthy metabolic status significantly increases KS risk, and combined effects can substantially elevate this risk. Previous studies have identified a broad range of KS risk factors, including biological factors, high sodium intake, metabolic disturbances, and genetic predispositions[10]. Observational studies suggest that vascular calcification may also increase KS risk[11].A growing number of studies indicate a positive association between CVD and KS, suggesting potential shared pathological mechanisms. Therefore, each component of CKM syndrome may influence KS formation.

To better understand these connections, the American Heart Association (AHA) introduced a model

classifying CKM syndrome into distinct stages[4]. Assessing the associations between the combined effects of these factors at various stages and KS prevalence is essential. However, few studies have explored the relationship between this new concept, CKM syndrome, and the KS stages. The aim of this study was to investigate the association between CKM syndrome stages and the prevalence of KS in a nationally representative sample of U.S. adults, utilizing data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2020.

Materials and methods

Study population

NHANES is a nationally representative cross-sectional survey conducted by the National Center for Health Statistics (NCHS), collecting health and nutrition data via complex sampling methods (data available at https://www.cdc.gov/nchs/nhanes). The study was approved by the NCHS Ethics Review Board (Protocols #2005-06, #2011-17, #2018-01); informed consent was obtained from all participants.

Fasting samples were used to measure key biomarkers (glucose, lipids) essential for CKM syndrome staging. From the NHANES 2007–2020 fasting subsample (n = 21,745), we excluded 2,772 participants with missing laboratory data or insufficient fasting duration. Of the remaining 18,973 individuals, we further excluded 3,215 under 20 years old, 147 pregnant participants, and 43 with missing KS data, yielding a final sample of 15,568 for analysis (Figure 1).

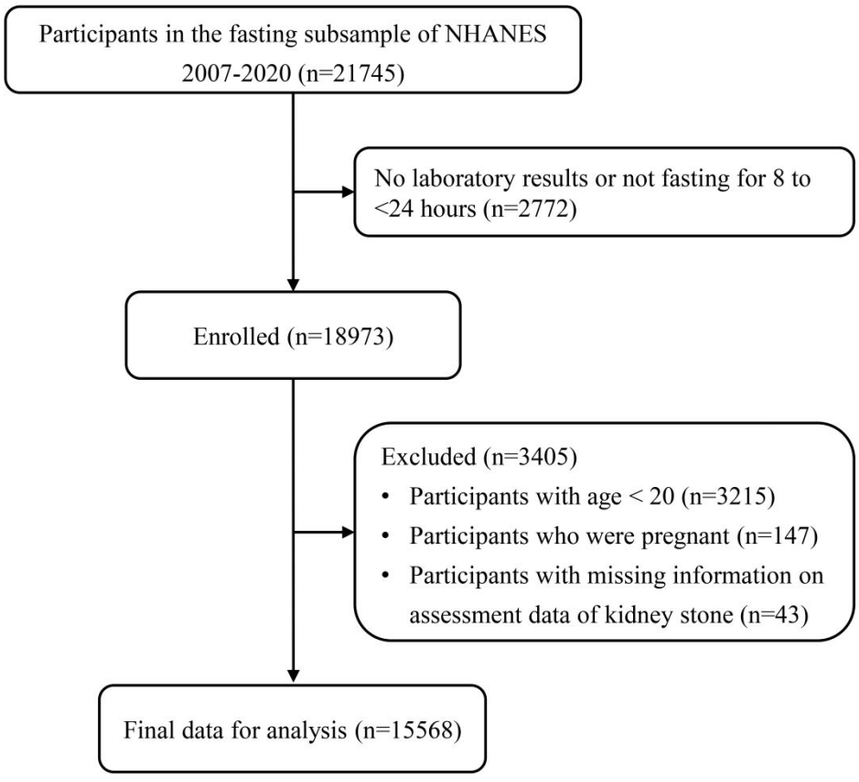

Figure 1: Flowchart of participant selection for the study.

Definition of KS

KS history was determined via self-report; participants who affirmed a prior KS diagnosis were classified accordingly. This method is validated, correctly identifying 97% of clinically diagnosed KS cases [12].

Assessment of CKM Syndrome Stages

CKM syndrome stages (0–4) were classified per the 2023 AHA Presidential Advisory on CKM Health[4]. Stage 0: individuals without CKM risk factors (e.g., hypertension, hyperlipidemia). Stage 1: overweight, obese, or dysfunctional adipose tissue without additional metabolic risk factors or CKD. Stage 2: presence of metabolic risk factors or CKD. Stage 3: high-risk CKD or high predicted 10-year CVD risk. Stage 4: established CVD (e.g., coronary artery disease). Detailed NHANES-adapted descriptions are in the Supplementary Material.

Assessment of Covariates

To control for confounding factors, covariates included: age (20–39, 40–59, ≥60 years), sex (male, female), race/ethnicity (non-Hispanic white, non-Hispanic black, other), education level (below high school, high school graduate, above high school), and family poverty-to-income ratio (PIR ≤1.0, 1.1–3.0, >3.0). Drinking status was categorized as nondrinkers, low-to-moderate, or heavy drinkers; smoking status as never, former, or current smoker. Physical activity (PA), based on self-report, was classified as inactive, insufficiently active, or active. Total energy intake and key biochemical markers (serum calcium, serum phosphorus, urinary creatinine) were divided into quartiles to account for metabolic variations. Detailed definitions are in the Supplementary Materials.

Statistical Analysis

Analyses followed NHANES guidelines with sample weights for the complex survey design, using the R "survey" package. Descriptive statistics summarized the study population: continuous variables as medians with interquartile ranges (IQR), categorical variables as weighted percentages. Mann-Whitney U tests compared continuous variables; chi-squared tests compared categorical variables. For CKM syndrome stages, Kruskal-Wallis tests were used, followed by Dunn's post-hoc tests when applicable.

Multivariable logistic regression models estimated the association between CKM syndrome stages

and KS prevalence, yielding odds ratios (ORs) with 95% confidence intervals (CIs). Subgroup analyses explored interactions between CKM stages and age, sex, race/ethnicity, smoking status, and physical activity. Statistical analyses were performed using R software (version 4.3.2), with significance defined at $P < 0.05$.

Results

Baseline Characteristics of Participants

Table 1 presents the survey-weighted baseline characteristics by KS status. Among 15,568 participants, 1,501 (9.64%) reported a history of KS. The median age was 48 years, with females comprising 51.32% of the cohort. Stone formers were significantly older; 38.12% were aged ≥60 years compared to 25.59% of non-stone formers ($P < 0.001$). Males had a higher prevalence of KS (53.27%) than females (46.73%) (P = 0.003). Participants with KS were more frequently classified into advanced CKM syndrome stages (Stages 3 and 4), with 24.42% versus 14.02% among non-stone formers ($P < 0.001$). Other covariates, including race/ethnicity, smoking status, drinking status, and physical activity, also showed significant differences between the groups.

Table 1. Survey-weighted characteristics of the general adult population by kidney stone in NHANES 2007–2020.

Characteristics	Overall	Non-Stone Former	Stone Former	*P* value
Participant, N	15568	14067	1501	
Age, years				<0.001
20-39	4893(35.91)	4618(37.40)	275(22.25)	
40-59	5323(37.27)	4799(37.01)	524(39.64)	
≥60	5352(26.82)	4650(25.59)	702(38.12)	
Sex, %				0.003
Female	8020(51.32)	7344(51.82)	676(46.73)	
Male	7548(48.68)	6723(48.18)	825(53.27)	
Race/ethnicity, %				<0.001
Non-Hispanic White	6333(66.13)	5553(65.19)	780(74.76)	
Non-Hispanic Black	3224(11.31)	3039(11.94)	185(5.54)	
Other race	6011(22.56)	5475(22.87)	536(19.70)	
Education level, %				0.852
Below high school	3752(16.24)	3382(16.18)	370(16.85)	
High school	3528(22.68)	3190(22.67)	338(22.74)	
Above high school	8288(61.08)	7495(61.15)	793(60.41)	
Family PIR, %				0.507
≤1.0	3409(15.40)	3092(15.53)	317(14.18)	
1.1–3.0	6577(36.32)	5943(36.28)	634(36.67)	
>3.0	5582(48.28)	5032(48.19)	550(49.15)	

Smoking status, %				0.027
Never smoker	8734(55.70)	7950(56.10)	784(52.09)	
Former smoker	3806(25.28)	3372(24.84)	434(29.31)	
Current smoker	3028(19.02)	2745(19.06)	283(18.60)	
Drinking status, %				< 0.001
Nondrinker	2067(10.53)	1867(10.44)	200(11.39)	
Former drinker	2052(11.88)	1800(11.41)	252(16.24)	
Current drinker	11449(77.59)	10400(78.16)	1049(72.37)	
Physical activity, %				< 0.001
Inactive	4064(21.88)	3592(21.23)	472(27.81)	
Insufficiently active	4885(32.66)	4440(32.79)	445(31.45)	
Active	6619(45.46)	6035(45.98)	584(40.74)	
Total energy intakes, kcal/day	2007.00 (1495.00,2655.00)	2007.00 (1493.00,2667.00)	2005.00 (1541.00,2585.00)	0.679
Serum calcium, mmol/L	2.33(2.28,2.40)	2.33(2.28,2.40)	2.33(2.28,2.38)	0.029
Serum phosphorus, mmol/L	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.03,1.26)	<0.001
Urinary creatinine, mg/dL	114.00(67.00,168.00)	113.00(66.00,168.00)	120.00(77.00,168.00)	0.006
CKM syndrome stage, %				<0.001
Stage 0	1457(11.83)	1390(12.45)	67(6.15)	
Stage 1	3211(23.11)	3014(23.91)	197(15.78)	
Stage 2	7735(50.02)	6968(49.62)	767(53.65)	
Stage 3	1385(5.87)	1198(5.53)	187(8.96)	
Stage 4	1780(9.17)	1497(8.49)	283(15.46)	

Abbreviations: PIR, poverty income ratio; CKM, cardiovascular-kidney-metabolic. Continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

Table 2 summarizes the survey-weighted characteristics across CKM syndrome stages. In Stage 0, 66.05% of participants were aged 20–39 years, whereas in Stage 4, 69.49% were aged ≥60 years ($P < 0.001$). A higher proportion of males was observed in advanced stages: 54.78% in Stage 4 compared to 32.69% in Stage 0 ($P < 0.001$). KS prevalence increased consistently with advancing CKM stages, rising from 5.10% in Stage 0 to 16.55% in Stage 4. As shown in Figure 2, the prevalence progressed as follows: 5.10% (Stage 0), 6.71% (Stage 1), 10.53% (Stage 2), 15.00% (Stage 3), and 16.55% (Stage 4), indicating a significant upward trend with increasing CKM syndrome severity ($P < 0.001$).

Table 2. Survey-weighted characteristics of the general adult population by CKM syndrome stages in NHANES 2007–2020.

Characteristics	CKM syndrome stage					*P* value
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Participant, N	1457	3211	7735	1385	1780	
Age, years						<0.001
20-39	996(66.05)	1676(53.78)	2138(30.22)	9(0.80)	74(5.53)	
40-59	382(28.56)	1134(35.22)	3345(46.34)	64(4.80)	398(24.98)	
≥60	79(5.39)	401(11.01)	2252(23.45)	1312(94.40)	1308(69.49)	
Sex, %						<0.001
Female	974(67.31)	1728(51.37)	3921(48.92)	608(48.92)	789(45.22)	
Male	483(32.69)	1483(48.63)	3814(51.08)	777(51.08)	991(54.78)	
Race/ethnicity, %						<0.001
Non-Hispanic White	657(70.46)	1159(62.34)	2886(64.89)	713(72.83)	918(72.65)	
Non-Hispanic Black	188(7.34)	686(12.58)	1672(11.54)	271(11.22)	407(12.03)	
Other race	612(22.20)	1366(25.08)	3177(23.57)	401(15.95)	455(15.32)	
Education level, %						<0.001
Below high school	194(9.48)	613(12.65)	1898(16.86)	470(25.14)	577(24.98)	
High school	258(16.68)	671(21.45)	1773(23.05)	369(29.35)	457(27.22)	
Above high school	1005(73.84)	1927(65.90)	4064(60.09)	546(45.50)	746(47.80)	
Family PIR, %						<0.001
≤1.0	271(12.78)	713(15.79)	1702(15.42)	306(16.63)	417(16.89)	
1.1–3.0	535(30.49)	1255(34.38)	3212(35.43)	685(47.18)	890(46.62)	
>3.0	651(56.74)	1243(49.83)	2821(49.15)	394(36.19)	473(36.49)	
Smoking status, %						<0.001
Never smoker	1004(65.82)	1980(60.01)	4372(55.25)	649(47.09)	729(39.83)	
Former smoker	185(15.70)	622(22.11)	1784(24.73)	544(40.90)	671(38.58)	
Current smoker	268(18.48)	609(17.88)	1579(20.02)	192(12.01)	380(21.60)	
Drinking status, %						<0.001
Nondrinker	185(9.86)	332(8.67)	1036(10.29)	265(18.90)	249(12.03)	
Former drinker	89(5.74)	251(7.36)	966(11.98)	337(23.05)	409(23.48)	
Current drinker	1183(84.40)	2628(83.97)	5733(77.73)	783(58.05)	1122(64.49)	
Physical activity, %						<0.001
Inactive	222(12.18)	569(16.28)	1915(21.59)	616(42.11)	742(37.13)	
Insufficiently active	470(31.79)	992(32.01)	2524(33.94)	397(29.85)	502(30.15)	
Active	765(56.02)	1650(51.70)	3296(44.46)	372(28.04)	536(32.72)	
Total energy intakes, kcal/day	1974.00 (1551.00,2624.00)	2098.00 (1588.00,2751.00)	2066.00 (1531.00,2709.00)	1666.00 (1263.00,2147.00)	1810.00 (1330.00,2360.00)	<0.001
Serum calcium, mmol/L	2.35(2.30,2.40)	2.33(2.28,2.38)	2.33(2.28,2.40)	2.35(2.28,2.40)	2.33(2.28,2.40)	<0.001
Serum phosphorus, mmol/L	1.23(1.13,1.32)	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.07,1.29)	<0.001
Urinary creatinine, mg/dL	102.00 (57.00,160.00)	118.00 (69.00,176.00)	115.00 (69.00,170.00)	99.00 (65.00,143.00)	108.00 (67.00,155.00)	<0.001
Kidney stone, %						<0.001
No	1390(94.90)	3014(93.29)	6968(89.47)	1198(85.00)	1497(83.45)	

Yes	67(5.10)	197(6.71)	767(10.53)	187(15.00)	283(16.55)

Abbreviations: PIR, poverty income ratio; CKM, cardiovascular-kidney-metabolic. Continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

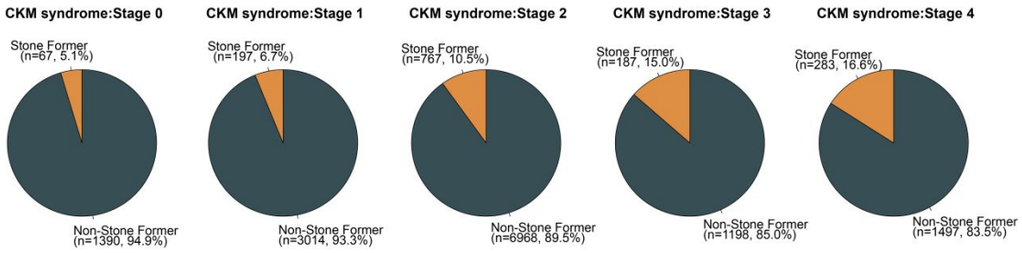

Figure 2: Prevalence of kidney stones across CKM syndrome stages.

Association between CKM syndrome stages and the prevalence of KS

Table 3 illustrates the odds ratios (ORs) for kidney stone (KS) prevalence across CKM syndrome stages. In the unadjusted model, KS likelihood rose progressively with advancing CKM stages, with Stage 4 showing almost 3.7 times the odds compared to Stage 0. This association remained robust in Model 1, which adjusted for age, sex, and race/ethnicity. The trend persisted in Model 2 with further adjustments for socioeconomic and lifestyle factors. In Model 3, even after additional adjustments for serum calcium, phosphorus, and creatinine, the ORs for KS prevalence continued to increase with CKM severity: 1.18 (95% CI: 0.83–1.68) for Stage 1, 1.72 (95% CI: 1.28–2.32) for Stage 2, 2.00 (95% CI: 1.29–3.10) for Stage 3, and 2.36 (95% CI: 1.64–3.40) for Stage 4. This indicates a significant and stepwise rise in KS prevalence with worsening CKM stages ($P_{trend} < 0.001$).

Table 3. OR (95% CIs) of the prevalence of kidney stone according to CKM syndrome stages among adults in NHANES 2007–2020.

	CKM syndrome stage					P_{trend}
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Crude	1.00 [Reference]	1.34(0.94,1.91)	2.19(1.64,2.93)	3.28(2.29,4.71)	3.69(2.68,5.09)	<0.001
Model 1	1.00 [Reference]	1.27(0.89,1.82)	1.84(1.37,2.48)	2.24(1.48,3.40)	2.63(1.87,3.72)	<0.001
Model 2	1.00 [Reference]	1.25(0.88,1.79)	1.80(1.34,2.42)	2.08(1.35,3.22)	2.45(1.71,3.51)	<0.001
Model 3	1.00	1.18(0.83,1.68)	1.72(1.28,2.32)	2.00(1.29,3.10)	2.36(1.64,3.40)	<0.001

[Reference]	)	)	)	)	1

Abbreviations: OR, Odd ratio; CI, confidence interval; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Model 1 was adjusted as age (20-39, 40-59, or ≥60), sex (male or female), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race); Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles); Model 3 was adjusted as model 2 plus serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles).

Stratified analysis

Table 4 presents stratified analyses of the association between CKM syndrome stage and KS prevalence. Among participants aged 20–59, Stage 4 was associated with over threefold increased odds of KS compared to Stage 0 (OR = 3.14, 95% CI: 2.08–4.73). In those aged ≥60 years, the association was weaker and nonsignificant (OR = 1.31, 95% CI: 0.45–3.80), with no significant age interaction (*P* for interaction = 0.482). Sex-stratified results were similar; in Stage 4, females and males had approximately 2.4 times the odds of KS, with no significant sex interaction (*P* for interaction = 0.299). Non-Hispanic Whites showed stronger associations (OR = 2.28, 95% CI: 1.45–3.60), with weaker trends in other ethnicities. Consistent patterns emerged across subgroups of family PIR, education level, smoking, drinking, and physical activity. Despite varying strengths, the association between CKM syndrome severity and KS prevalence remained consistent across these groups.

Table 4. Stratified analyses of the associations between CKM syndrome stage and the prevalence of kidney stone among adults in NHANES 2007–2020.

Subgroups	N	CKM syndrome stage					*P-int*
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Age, years							0.482
20-59	10216	1 [Reference]	1.35 (0.92-1.98)	2.10 (1.51-2.91)	2.79 (0.86-9.10)	3.14 (2.08-4.73)	
≥ 60	5352	1 [Reference]	0.61 (0.20-1.89)	0.96 (0.32-2.88)	1.15 (0.39-3.41)	1.31 (0.45-3.80)	
Sex, %							0.299
Female	8020	1 [Reference]	1.33 (0.85-2.07)	1.82 (1.21-2.74)	1.99 (1.05-3.77)	2.36 (1.40-4.00)	
Male	7548	1 [Reference]	1.09 (0.56-2.15)	1.78 (0.99-3.20)	2.09 (1.04-4.21)	2.47 (1.34-4.55)	
Race, %							0.351
Non-Hispanic White	6333	1 [Reference]	1.23 (0.79-1.92)	1.68 (1.16-2.43)	2.05 (1.17-3.57)	2.28 (1.45-3.60)	

Non-Hispanic Black	3224	1 [Reference]	0.79 (0.36-1.70)	1.50 (0.70-3.18)	1.94 (0.79-4.77)	1.53 (0.56-4.14)	
Other race	6011	1 [Reference]	1.10 (0.62-1.94)	1.91 (1.11-3.31)	1.66 (0.84-3.28)	3.02 (1.60-5.69)	
Family PIR, %							0.687
≤1.0	3409	1 [Reference]	1.75 (0.76-4.00)	2.42 (1.14-5.18)	3.02 (1.05-8.72)	4.37 (1.90-10.04)	
1.1–3.0	6577	1 [Reference]	1.34 (0.78-2.30)	1.84 (1.13-3.00)	1.94 (1.14-3.33)	2.56 (1.59-4.11)	
>3.0	5582	1 [Reference]	1.02 (0.62-1.67)	1.54 (1.00-2.39)	2.07 (1.13-3.80)	1.88 (1.05-3.37)	
Education level, %							0.571
Below high school	3752	1 [Reference]	1.72 (0.66-4.47)	3.10 (1.31-7.33)	2.78 (1.00-7.73)	4.34 (1.78-10.56)	
High school	3528	1 [Reference]	0.92 (0.41-2.07)	1.21 (0.59-2.49)	1.19 (0.47-3.03)	1.42 (0.67-3.01)	
Above high school	8288	1 [Reference]	1.22 (0.77-1.93)	1.75 (1.19-2.57)	2.53 (1.48-4.32)	2.47 (1.49-4.09)	
Smoking status, %							0.266
Nonsmokers	8734	1 [Reference]	1.47 (0.88-2.46)	2.29 (1.46-3.62)	2.40 (1.28-4.51)	3.61 (2.04-6.39)	
Former smokers	3806	1 [Reference]	0.84 (0.40-1.73)	1.17 (0.61-2.25)	1.73 (0.78-3.85)	1.63 (0.83-3.20)	
Current smokers	3028	1 [Reference]	0.93 (0.47-1.83)	1.23 (0.63-2.42)	1.23 (0.43-3.49)	1.41 (0.61-3.26)	
Drinking status, %							0.336
Nondrinker	2067	1 [Reference]	0.58 (0.20-1.74)	1.50 (0.73-3.11)	1.86 (0.66-5.24)	1.95 (0.84-4.52)	
Low-to-moderate drinker	2052	1 [Reference]	1.74 (0.51-5.94)	2.40 (0.87-6.66)	2.08 (0.63-6.81)	2.70 (0.82-8.91)	
Heavy drinker	11449	1 [Reference]	1.23 (0.82-1.87)	1.72 (1.21-2.43)	2.18 (1.31-3.63)	2.52 (1.63-3.88)	
Physical activity, %							0.575
Inactive	4064	1 [Reference]	1.19 (0.48-2.97)	1.47 (0.61-3.56)	1.49 (0.55-4.05)	2.24 (0.89-5.63)	
Insufficiently active	4885	1 [Reference]	1.00 (0.48-2.11)	2.06 (1.13-3.75)	2.86 (1.37-5.97)	2.69 (1.27-5.71)	
Active	6619	1 [Reference]	1.27 (0.81-1.99)	1.65 (1.10-2.49)	2.08 (1.15-3.78)	2.09 (1.24-3.51)	
Serum calcium, mmol/L							0.395
Quartile 1	4717	1 [Reference]	2.10 (1.06-4.16)	2.93 (1.59-5.41)	2.85 (1.22-6.65)	3.01 (1.35-6.70)	
Quartile 2	3638	1 [Reference]	1.20 (0.60-2.41)	1.66 (0.90-3.05)	2.01 (0.77-5.26)	3.05 (1.34-6.94)	
Quartile 3	3361	1 [Reference]	0.57 (0.29-1.11)	1.24 (0.71-2.17)	1.63 (0.75-3.58)	1.73 (0.80-3.72)	
Quartile 4	3852	1 [Reference]	1.24 (0.55-2.78)	1.59 (0.86-2.95)	1.98 (0.91-4.35)	2.41 (1.27-4.57)	
Serum phosphorus, mmol/L							0.408
Quartile 1	4635	1 [Reference]	1.16 (0.62-2.16)	1.52 (0.89-2.60)	1.52 (0.74-3.12)	2.23 (1.15-4.35)	
Quartile 2	3543	1	1.76 (0.67-	2.15 (0.82-	4.16 (1.27-	3.10 (1.00-	

		[Reference]	4.63)	5.65)	13.63)	9.60)
Quartile 3	4131	1 [Reference]	1.48 (0.75-2.92)	2.28 (1.20-4.36)	2.24 (0.83-6.01)	3.20 (1.32-7.75)
Quartile 4	3259	1 [Reference]	0.53 (0.26-1.08)	1.38 (0.77-2.48)	1.63 (0.72-3.69)	1.97 (1.02-3.83)
Urinary creatinine, mg/dL						0.393
Quartile 1	3913	1 [Reference]	1.58 (0.76-3.28)	1.60 (0.85-3.03)	2.19 (0.95-5.07)	2.89 (1.31-6.39)
Quartile 2	4038	1 [Reference]	1.04 (0.54-1.98)	1.35 (0.80-2.28)	1.69 (0.78-3.66)	2.06 (1.09-3.87)
Quartile 3	3750	1 [Reference]	1.83 (0.89-3.77)	2.85 (1.45-5.59)	2.85 (1.22-6.65)	3.12 (1.60-6.08)
Quartile 4	3867	1 [Reference]	0.68 (0.33-1.42)	1.43 (0.77-2.64)	1.80 (0.74-4.39)	1.69 (0.78-3.67)

Abbreviations: OR, Odd ratio; CI, confidence interval; PIR, poverty-to-income ratio; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Analyses were adjusted for age (20-39, 40-59, or ≥60), sex (male or female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race), education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles), serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles) when they were not the strata variables. *p-int*, p for interaction.

Discussion

This study explored the relationship between CKM syndrome stages and the prevalence of KS among 15,568 U.S. adults using data from the NHANES 2007–2020. We found that participants with CKM syndrome had significantly higher odds of KS as CKM stage advanced. Moreover, the association between the CKM syndrome stage and KS prevalence was consistent in the fully adjusted models.

Both CKM syndrome and KS are systemic conditions affecting multiple organs. This study shows KS prevalence is closely linked to advanced CKM syndrome, characterized by insulin resistance, obesity, dyslipidemia, and hypertension. These contribute to stone formation and reflect metabolic dysfunction. CKM syndrome begins early in life[13], inducing dysfunctional adipose tissue, inflammation, oxidative stress, and insulin resistance[14], leading to hypertension, hypertriglyceridemia, metabolic syndrome, and type 2 diabetes[4]. As these conditions progress, they burden the kidneys, causing CKD and worsening CKM syndrome[3].

Metabolic syndrome is a known risk factor for KS development. Type 2 diabetes patients have an elevated risk of urinary KS due to increased urinary oxalate excretion, enhancing calcium oxalate stone formation[15]. Their urinary profiles—high oxalate excretion and low pH—make them more

prone to uric acid and calcium oxalate stones[15]. Uric acid stone formers face a higher risk of diabetes and glucose intolerance than non-stone formers[16];increasing HbA1c levels correlate with lower urinary pH, further contributing to KS risk[17].

Obesity is another significant factor associated with KS. Excess caloric intake results in greater metabolic waste and altered urinary composition[18]. Studies show that waist circumference and body mass index are linked to higher KS risk among adults over 46 years of age[19]. In obese individuals, insulin resistance impairs renal ammonium excretion[7],and obesity induces a pro-inflammatory state contributing to KS via oxidative stress and altered renal function. Dyslipidemia is also linked to KS, particularly uric acid stone formation[20]. Masterson et al. found individuals with dyslipidemia are over twice as likely to develop KS[21], and Inci et al. reported that KS formers have significantly higher serum lipid levels[22].

A large longitudinal cohort study in Taiwan confirmed a strong relationship between metabolic syndrome and KS formation, with hypertension identified as the strongest predictor of metabolic syndrome components[23]. Metabolic dysfunction has been independently associated with a higher risk of KS, especially in individuals with both obesity and metabolic dysfunction[24]. A meta-analysis confirmed a positive correlation between the number of metabolic syndrome components (such as hypertension, obesity, and dyslipidemia) and risk of KS development[25]. In 694 aging males, Yung et al. found metabolic syndrome and particularly hypertension strongly associated with nephrolithiasis[26]. Kohjimoto et al. reported hypertension and dyslipidemia significantly linked to KS severity, while other metabolic traits showed less consistent associations [27]. While relationships between CKM syndrome components and KS vary across populations, our study found no significant demographic interactions, indicating a consistent association between CKM stages and KS prevalence across these groups.

KS and CKD are closely related, each potentially exacerbating the other. Stone formation can lead to long-term kidney damage, inducing CKD[28]. Patients with CKD often exhibit altered urinary excretion of calcium, oxalate, phosphate, and uric acid—key contributors to stone formation[28]. Impaired kidney function diminishes oxalate filtration and excretion, leading to its accumulation in the bloodstream[29]. The Chronic Renal Insufficiency Cohort study found that as estimated glomerular filtration rate (eGFR) declined in CKD stages 2–4, urinary oxalate excretion decreased[30], increasing stone risk due to metabolic imbalance. However, some studies suggest CKD may offer protection against KS[31]. One study observed that CKD patients with average creatinine clearance

of 35–38 mL/min exhibited hypocitraturia without significant differences in other components[32]. since citrate inhibits calcium stone formation, this could influence stone risk. A single-center study indicated that urinary components involved in stone formation were positively associated with eGFR[33], implying that worse kidney function might reduce stone-forming constituents. Although current data suggest a connection, more comprehensive studies are needed to establish a clear pattern of how worsening kidney function affects KS development.

Several large-scale epidemiological studies report that individuals with a history of KS have a higher risk of myocardial infarction, coronary heart disease, and stroke compared to those without stones[34, 35]. Reiner's longitudinal study found that KS history is associated with greater carotid artery wall thickness[36]. His et al. identified a significant association between recurrent KS formation and coronary artery calcium (CAC), especially in those with higher CAC scores[37], suggesting a link between recurrent KS and increased coronary artery calcification. CVD-related metabolic factors such as cholesterol, phospholipids, and uric acid are associated with KS pathogenesis [38]. Evidence suggests that KS formers with CVD have lower renal alkali excretion and higher acid retention[39]. Hamono et al. found that CVD risk factors—including smoking, hypertension, and overweight—are positively correlated with calcium oxalate stone risk[40]. Abdominal aortic calcification significantly correlates with hypocitraturia; stone formers have notably lower urinary citrate excretion[41].These findings suggest that hypocitraturia may be a common mechanism for both CVD and KS.

The association between CKM syndrome and KS prevalence involves several interconnected mechanisms. Patients with CKM syndrome are at higher risk of developing both calcium oxalate and uric acid stones, with urinary pH playing a critical role in stone composition; acidic urine promotes uric acid stones, while alkaline urine favors calcium phosphate stones. Insulin resistance impairs renal ammoniogenesis in proximal tubules, reducing ammonia production and lowering urinary pH[42], increasing uric acid stone risk. The inflammatory response also contributes to KS and CKM syndrome progression[43]; elevated urinary oxalate levels—a key risk factor for calcium oxalate stones—are influenced by inflammatory molecules like monocyte chemoattractant protein 1 and immune cell activity[43]. Both KS formation and atherosclerotic plaque development involve macrophage recruitment, releasing inflammatory mediators that cause tissue damage and calcium deposition[44]. Metabolic syndrome may also increase oxalate excretion[27]; elevated urinary oxalate harms renal parenchyma and may be reabsorbed into proximal tubules via passive diffusion[30]. The individual traits of CKM syndrome independently influence stone formation risk, and cumulatively further increase the risk of both calcium oxalate and uric acid stones. Future studies are needed to clarify

these pathways and identify additional mechanisms.

To our knowledge, this is the first study to examine the relationship between CKM syndrome and KS in a large population from NHANES. CKM syndrome is a relatively new clinical concept with stages based on recent guidelines. We analyzed CKM syndrome stages (0–4) and KS prevalence in a broad population, finding a clear and progressive increase in KS prevalence with advancing CKM stages.

However, this study has limitations. First, its cross-sectional design prevents inference of causality or temporal relationships between CKM syndrome and KS development. Longitudinal and mechanistic studies are needed to confirm this hypothesis. Second, some data were self-reported, such as KS history, which may be subject to recall bias or misreporting. Third, despite multivariate adjustments, unmeasured confounders might have influenced the observed associations. Lastly, our study included only U.S. adults, limiting generalizability to other settings or populations.

Conclusions

This study demonstrates a clear and progressive association between advancing CKM syndrome stages and increased KS prevalence in a nationally representative U.S. adult population. Individuals with more advanced CKM stages are at higher risk of developing KS. These findings underscore the critical importance of early detection and effective management of CKM syndrome to mitigate KS risk and burden. Further research is needed to elucidate the underlying mechanisms driving this association and to develop targeted prevention strategies for at-risk populations.

Figure legends

Figure 1: Flowchart of participant selection for the study.

Figure 2: Prevalence of kidney stones across CKM syndrome stages.

Use of AI and AI-assisted technologies statement

AI has not been used in the writing process.

Author contributions

DW W: Conceived and designed the study; drafted the initial manuscript.
JJ T: Collected and analyzed the data and assisted in writing and editing the manuscript.
F S: Analyzed data and organized data.
DG Z: Supervised the research and was responsible for the manuscript revision and final approval.
GL L: Provided research resources; responsible for project management.

Abbreviations

CKM, cardiovascular-kidney-metabolic; KS, kidney stone; NHANES, National Health and Nutrition Examination Survey; ORs, odds ratio; CIs, confidence interval; AHA, American Heart Association; CVD, cardiovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; NCHS, National Center for Health Statistics; PIR, poverty-to-income ratio; PA, physical activity; IQRs, interquartile range.

Declaration

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We appreciate the contributions of the participants to the NHANES data.

Disclosure Statement

The authors have no competing interests to declare.

Ethics Statement

All participants provided written informed consent and study procedures were approved by the National Center for Health Statistics Research Ethics Review Board (Protocol Number: Protocol #2011-17).

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Data Availability

NHANES data described in this manuscript are available at https://wwwn.cdc.gov/nchs/nhan

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Online Supplementary Material

Association of Cardiovascular-Kidney-Metabolic Syndrome with Kidney Stones: A Population-based Study

Materials and methods

Assessment of cardiovascular-kidney-metabolic syndrome stages

Cardiovascular-kidney-metabolic (CKM) syndrome stages were classified using NHANES 2017-2018 data, in line with the 2023 AHA Presidential Advisory on CKM Health [1]. This classification system was specifically adapted to the NHANES dataset for this analysis. Definitions were adapted to the available data as follows:

CKM Stage 0: Participants with a normal BMI (<25 kg/m²), waist circumference (<88 cm for women, <102 cm for men), normoglycemia (fasting glucose <100 mg/dL, HbA1c <5.7%), normal blood pressure (systolic <130 mmHg, diastolic <80 mmHg), a healthy lipid profile (triglycerides <135 mg/dL), and no signs of CKD or cardiovascular disease (CVD).

CKM Stage 1: Individuals with an elevated BMI (≥25 kg/m²), increased waist circumference (≥88 cm for women, ≥102 cm for men), or prediabetes (HbA1c 5.7%-6.4% or fasting glucose 100-125 mg/dL), but without other metabolic risk factors or CKD.

CKM Stage 2: Participants with additional metabolic risk factors or moderate-to-high-risk CKD, as defined by KDIGO guidelines [2]. Risk factors included elevated triglycerides (≥135 mg/dL), hypertension, diabetes, or metabolic syndrome, characterized by at least three of the following:

increased waist circumference, low HDL (men <40 mg/dL, women <50 mg/dL), high triglycerides (≥150 mg/dL), elevated blood pressure (systolic ≥130 mmHg, diastolic ≥80 mmHg), or prediabetes.

CKM Stage 3: Those classified with very-high-risk CKD based on KDIGO criteria, or with a high 10-year CVD risk (≥20%), calculated using the AHA PREVENT risk equations (based on recommended thresholds [https://professional.heart.org/en/guidelines-and-statements/prevent-calculator]) [3].

CKM Stage 4: Individuals with self-reported established CVD, including coronary heart disease, angina, myocardial infarction, heart failure, or stroke. Data for atrial fibrillation and peripheral artery disease were unavailable and not included.

Assessment of Other Covariates

This study included several confounding variables such as family poverty-to-income ratio (PIR), drinking status, smoking status, physical activity, and total energy intake, which were defined as follows:

Family poverty income ratio Income was assessed using the poverty income ratio (PIR, the ratio of family income divided by a poverty threshold specific for family size using guidelines from the US Department of Health and Human Services) and categorized as ≤1.0, 1.1-3.0 and >3.0 [4].

Drinking status Drinking status was classified as nondrinker, low-to-moderate drinker (<2 drinks/day in men and <1 drink/day in women), or heavy drinker (≥2 drinks/day in men and ≥1 drinks/day in women) [5].

Smoking status Never smokers were classified as those who reported smoking <100 cigarettes during their lifetime. Those who smoked >100 cigarettes in their lifetime were considered as current smokers, and those who smoked >100 cigarettes and had quit smoking were considered as former smokers [5].

Physical activity Physical activity was categorized as inactive group (no leisure-time physical activity), insufficiently active group (leisure time moderate activity 1–5 times per week with MET ranging from 3 to 6 or leisure-time vigorous activity 1–3 times per week with MET >6), or active group (those who had more leisure-time moderate-or-vigorous activity than above) [6].

Dietary total energy intakes Dietary intake was assessed through two 24-hour recalls—one conducted in person at the NHANES Mobile Examination Center (MEC) and the second by telephone 3 to 10 days later. Participants reported all foods and beverages consumed during the 24-hour period, and total energy intake was estimated using the USDA Automated Multiple-Pass Method (AMPM) and analyzed via the Food and Nutrient Database for Dietary Studies (FNDDS). The average of the two recalls was used for analysis. Further details on dietary assessment can be found at: https://wwwn.cdc.gov/nchs/nhanes/tutorials/dietaryanalyses.aspx

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Association of Cardiovascular-Kidney-Metabolic Syndrome Stages with Kidney Stone Prevalence: A Cross-Section Study

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Abstract

Background: The prevalence of kidney stones (KS) has been increasing globally, and their association with cardiovascular disease and metabolic syndrome suggests a shared underlying pathophysiology. However, the impact of different stages of cardiovascular-kidney-metabolic (CKM) syndrome on KS prevalence remains unclear.

Objective: This study aimed to investigate the association between the stages of cardiovascular-kidney-metabolic (CKM) syndrome and the prevalence of kidney stones (KS) in a nationally representative sample of adults in the United States.

Methods: A total of 15,568 participants aged ≥20 years were included in the National Health and Nutrition Examination Survey 2007–2020 fasting subsample. CKM syndrome stages (0–4) were defined based on the 2023 American Heart Association Presidential Advisory on CKM Health. The KS history was determined using self-reported data. Multivariable logistic regression models were used to assess the association between the CKM syndrome stage and KS prevalence.

Results: Of the 15,568 participants, 1,501 (9.64%) reported a history of KS. The KS prevalence increased progressively with advancing CKM stage, rising from 5.10% in stage 0 to 16.55% in stage 4 ($P < 0.001$). In the fully adjusted model, the odds ratios (ORs) for KS were 1.18 (95% confidence interval [CI]: 0.83–1.68) for Stage 1, 1.72 (95% CI: 1.28–2.32) for Stage 2, 2.00 (95% CI: 1.29–3.10) for Stage 3, and 2.36 (95% CI: 1.64–3.40) for Stage 4, compared to Stage 0 (P for trend < 0.001). Stratified analyses revealed no significant interactions between age, sex, race/ethnicity, or other subgroups.

Conclusion: This study demonstrated a significant stepwise increase in KS prevalence with the advancing stages of CKM syndrome. These findings highlight the importance of monitoring and managing CKM syndromes to mitigate the risks of KS.

Keywords: cardiovascular disease; kidney disease; metabolic syndrome; kidney stones; National Health and Nutrition Examination Survey.

Strengths of the Study:

Novel Approach: This is the first study to explore CKM syndrome stages in relation to kidney stones, offering new insights for future research.

Large Sample Size: This study utilized a large, nationally representative sample from NHANES, enhancing generalizability.

Limitations of the Study:

Cross-Sectional Design: The cross-sectional design prevents inference of causality between CKM syndrome and kidney stone development.

Limited Generalizability: The study included only U.S. adults, limiting the applicability of results to other populations or regions.

Introduction

Kidney stones (KS) are hard mineral deposits forming in the renal calyces and pelvis when urine concentrations of substances like calcium, oxalate, uric acid, or phosphate become high enough to crystallize[1]. KS affects 10.1% of the U.S. population[2]. Recent research suggests KS is a systemic disorder linked to chronic diseases such as cardiovascular diseases (CVD), diabetes, and obesity, rather than being limited to the kidneys. Stone formation is a complex process influenced by genetic, metabolic, and environmental factors[3].

Cardiovascular-Kidney-Metabolic (CKM) syndrome, recently defined by the American Heart Association (AHA), represents a systemic disorder characterized by the pathophysiological interplay among metabolic risk factors (e.g., obesity, type 2 diabetes, hypertension, dyslipidemia, and insulin resistance), chronic kidney disease (CKD), and CVD[4]. These conditions share common underlying mechanisms, including systemic inflammation and metabolic dysfunction, which create a vicious cycle of organ damage and disease progression. The presence of one condition often exacerbates others, leading to increased risks of adverse outcomes, morbidity, and mortality[5–7]. CKM syndrome encompasses individuals at risk for CVD due to metabolic or kidney-related factors, as well as those with established CVD complicated by these conditions. Furthermore, social determinants of health, such as socioeconomic status and environmental factors, exacerbate biological risks and create barriers to effective lifestyle modification and care[8]. This integrated framework underscores the need for interdisciplinary approaches to address the complex mechanisms, clinical heterogeneity, and management challenges associated with CKM syndrome. In this study, we explore the association between CKM syndrome stages and KS prevalence, as both conditions are systemic and share underlying metabolic disturbances.

CKM syndrome comprises interconnected risk factors that elevate the likelihood of developing CVD, type 2 diabetes, and other health complications. Metabolic diseases such as obesity, diabetes mellitus (DM), and hypertension are associated with an increased risk of KS[9]. An 8-year follow-up study found a correlation between high blood pressure and KS development, with the risk further heightened when hypertension coexists with overweight conditions[10]. These factors can alter urine composition, metabolic processes, and kidney function, promoting stone formation. Specifically, increased acid excretion, low citrate levels, and high calcium excretion create a conducive environment for KS[11].

Emerging evidence supports the association between KS and various metabolic risk factors.

Unhealthy metabolic status significantly increases KS risk, and combined effects can substantially elevate this risk. Previous studies have identified a broad range of KS risk factors, including biological factors, high sodium intake, metabolic disturbances, and genetic predispositions[12]. Observational studies suggest that vascular calcification may also increase KS risk[13].A growing number of studies indicate a positive association between CVD and KS, suggesting potential shared pathological mechanisms. Therefore, each component of CKM syndrome may influence KS formation.

To better understand these connections, the American Heart Association (AHA) introduced a model classifying CKM syndrome into distinct stages[7]. Assessing the associations between the combined effects of these factors at various stages and KS prevalence is essential. However, few studies have explored the relationship between this new concept, CKM syndrome, and the KS stages. The aim of this study was to investigate the association between CKM syndrome stages and the prevalence of KS in a nationally representative sample of U.S. adults, utilizing data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2020.

Materials and methods

Study population

NHANES is a nationally representative cross-sectional survey conducted by the National Center for Health Statistics (NCHS), collecting health and nutrition data via complex sampling methods (data available at https://www.cdc.gov/nchs/nhanes). The study protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (Protocols #2005-06, #2011-17, #2018-01) and Ruijin Hospital(2024-177), and all participants provided written informed consent.

Fasting samples were used to measure key biomarkers (glucose, lipids) essential for CKM syndrome staging. From the NHANES 2007–2020 fasting subsample (n = 21,745), we excluded 2,772 participants with missing laboratory data or insufficient fasting duration. Of the remaining 18,973 individuals, we further excluded 3,215 under 20 years old, 147 pregnant participants, and 43 with missing KS data, yielding a final sample of 15,568 for analysis (Figure 1).

Definition of KS

KS history was determined through self-reported data. Participants were classified as having a KS history if they affirmed a prior diagnosis of KS by a healthcare professional in response to the questionnaire item, “Have you/Has sample person (SP) ever had kidney stones?”. Additionally, recurrence of KS was defined as having experienced two or more episodes of passing kidney stones, based on the response to “How many times have you/has SP passed a kidney stone?”. This self-report

method has been validated in prior studies, demonstrating a 97% accuracy rate in identifying clinically diagnosed KS cases [14].

Assessment of CKM Syndrome Stages

CKM syndrome stages (0–4) were classified according to the 2023 AHA Presidential Advisory on CKM Health[7], with adaptations for NHANES data. The stages were defined as follows: Stage 0: No CKM risk factors (e.g., absence of hypertension, hyperlipidemia, or metabolic abnormalities). Stage 1: Overweight, obesity, or dysfunctional adipose tissue without additional metabolic risk factors or CKD. Stage 2: Presence of metabolic risk factors (e.g., hypertension, dyslipidemia, insulin resistance) or CKD. Stage 3: High-risk CKD (e.g., eGFR <60 mL/min/1.73 m² or albuminuria ≥300 mg/g) or a high predicted 10-year CVD risk (≥20% based on validated risk scores). Stage 4: Established CVD (e.g., coronary artery disease, heart failure, or stroke). Detailed NHANES-adapted definitions for each stage, including specific criteria and thresholds, are provided in the Supplementary Material.

Assessment of Covariates

To account for potential confounding factors, the following covariates were included. Demographics: Age (categorized as 20–39, 40–59, ≥60 years), sex (male, female), and race/ethnicity (non-Hispanic white, non-Hispanic black, other). Socioeconomic Status: Education level (below high school, high school graduate, above high school) and family poverty-to-income ratio(PIR)(PIR ≤1.0, 1.1–3.0, >3.0). Lifestyle Factors: Drinking status: nondrinkers, low-to-moderate drinkers, or heavy drinkers (based on standard alcohol consumption thresholds); Smoking status: Never, former, or current smoker; Physical activity (PA): Classified as inactive, insufficiently active, or active based on self-reported adherence to physical activity guidelines. Biochemical and Nutritional Markers: Serum calcium, serum phosphorus, and urinary creatinine levels were divided into quartiles to account for metabolic variations; Total energy intake was assessed using 24-hour dietary recall data and categorized into quartiles. Detailed definitions and measurement protocols for all covariates are provided in the Supplementary Materials.

Statistical Analysis

All analyses adhered to NHANES guidelines, incorporating sample weights to account for the complex survey design, and were performed using the R "survey" package (version 4.3.2). Continuous variables were summarized as medians with interquartile ranges (IQR), while categorical variables were expressed as weighted percentages. Group comparisons were performed using the Mann-Whitney U test or Kruskal-Wallis H test for continuous variables with non-normal distributions and ordinal categorical variables, while the Chi-square test was applied to nominal categorical variables.

Multivariable logistic regression models estimated the association between CKM stages and KS prevalence, adjusting for covariates, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses explored interactions between CKM stages and key variables (age, sex, race/ethnicity, smoking status, and physical activity). A two-sided P <0.05 was considered statistically significant.

Patient and Public Involvement Statement

None

Results

Baseline Characteristics of Participants

Table 1 presents the survey-weighted baseline characteristics by KS status. Among 15,568 participants, 1,501 (9.64%) reported a history of KS. The median age was 48 years, with females comprising 51.32% of the cohort. Stone formers were significantly older; 38.12% were aged ≥60 years compared to 25.59% of non-stone formers ($P < 0.001$). Males had a higher prevalence of KS (53.27%) than females (46.73%) (P = 0.003). Participants with KS were more frequently classified into advanced CKM syndrome stages (Stages 3 and 4), with 24.42% versus 14.02% among non-stone formers ($P < 0.001$). Other covariates, including race/ethnicity, smoking status, drinking status, and physical activity, also showed significant differences between the groups.

Table 1. Survey-weighted characteristics of the general adult population by kidney stone in NHANES 2007–2020.

Characteristics	Overall	Non-Stone Former	Stone Former	*P* value
Participant, N	15568	14067	1501	
Age, years				<0.001
20-39	4893(35.91)	4618(37.40)	275(22.25)	
40-59	5323(37.27)	4799(37.01)	524(39.64)	
≥60	5352(26.82)	4650(25.59)	702(38.12)	
Sex, %				0.003
Female	8020(51.32)	7344(51.82)	676(46.73)	
Male	7548(48.68)	6723(48.18)	825(53.27)	
Race/ethnicity, %				<0.001
Non-Hispanic White	6333(66.13)	5553(65.19)	780(74.76)	
Non-Hispanic Black	3224(11.31)	3039(11.94)	185(5.54)	
Other race	6011(22.56)	5475(22.87)	536(19.70)	
Education level, %				0.604
Below high school	3752(16.24)	3382(16.18)	370(16.85)	
High school	3528(22.68)	3190(22.67)	338(22.74)	

Above high school	8288(61.08)	7495(61.15)	793(60.41)	
Family PIR, %				0.431
≤1.0	3409(15.40)	3092(15.53)	317(14.18)	
1.1–3.0	6577(36.32)	5943(36.28)	634(36.67)	
>3.0	5582(48.28)	5032(48.19)	550(49.15)	
Smoking status, %				0.018
Never smoker	8734(55.70)	7950(56.10)	784(52.09)	
Former smoker	3806(25.28)	3372(24.84)	434(29.31)	
Current smoker	3028(19.02)	2745(19.06)	283(18.60)	
Drinking status, %				0.002
Nondrinker	2067(10.53)	1867(10.44)	200(11.39)	
Former drinker	2052(11.88)	1800(11.41)	252(16.24)	
Current drinker	11449(77.59)	10400(78.16)	1049(72.37)	
Physical activity, %				< 0.001
Inactive	4064(21.88)	3592(21.23)	472(27.81)	
Insufficiently active	4885(32.66)	4440(32.79)	445(31.45)	
Active	6619(45.46)	6035(45.98)	584(40.74)	
Total energy intakes, kcal/day	2007.00 (1495.00,2655.00)	2007.00 (1493.00,2667.00)	2005.00 (1541.00,2585.00)	0.679
Serum calcium, mmol/L	2.33(2.28,2.40)	2.33(2.28,2.40)	2.33(2.28,2.38)	0.029
Serum phosphorus, mmol/L	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.03,1.26)	<0.001
Urinary creatinine, mg/dL	114.00(67.00,168.00)	113.00(66.00,168.00)	120.00(77.00,168.00)	0.006
Fasting blood glucose, mg/dL	100.00(93.00,109.00)	100.00(93.00,109.00)	103.000(95.00,115.00)	<0.001
Hemoglobin A1c, %	5.50(5.20,5.80)	5.40(5.20,5.80)	5.600(5.30,6.10)	<0.001
LDL-cholesterol, mg/dL	111.00(89.00,135.00)	111.00(89.00,135.00)	113.00(91.000,135.00)	0.427
HDL- cholesterol, mg/dL	51.000(43.00,63.00)	52.00(43.00,63.00)	48.00(41.00,59.00)	<0.001
CKM syndrome stage, %				<0.001
Stage 0	1457(11.83)	1390(12.45)	67(6.15)	
Stage 1	3211(23.11)	3014(23.91)	197(15.78)	
Stage 2	7735(50.02)	6968(49.62)	767(53.65)	
Stage 3	1385(5.87)	1198(5.53)	187(8.96)	
Stage 4	1780(9.17)	1497(8.49)	283(15.46)	

Abbreviations: PIR, poverty income ratio; LDL, low density lipoprotein; HDL, high density lipoprotein; CKM, cardiovascular-kidney-metabolic. Continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

Table 2 summarizes the survey-weighted characteristics across CKM syndrome stages. In Stage 0, 66.05% of participants were aged 20–39 years, whereas in Stage 4, 69.49% were aged ≥60 years ($P < 0.001$). A higher proportion of males was observed in advanced stages: 54.78% in Stage 4 compared to 32.69% in Stage 0 ($P < 0.001$). KS prevalence increased consistently with advancing CKM stages, rising from 5.10% in Stage 0 to 16.55% in Stage 4. As shown in Figure 2, the prevalence progressed as follows: 5.10% (Stage 0), 6.71% (Stage 1), 10.53% (Stage 2), 15.00% (Stage 3), and 16.55% (Stage 4), indicating a significant upward trend with increasing CKM syndrome severity ($P < 0.001$).

Table 2. Survey-weighted characteristics of the general adult population by CKM syndrome stages in NHANES 2007–2020.

Characteristics	CKM syndrome stage					*P* value
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Participant, N	1457	3211	7735	1385	1780	
Age, years						<0.001
20-39	996(66.05)	1676(53.78)	2138(30.22)	9(0.80)	74(5.53)	
40-59	382(28.56)	1134(35.22)	3345(46.34)	64(4.80)	398(24.98)	
≥60	79(5.39)	401(11.01)	2252(23.45)	1312(94.40)	1308(69.49)	
Sex, %						<0.001
Female	974(67.31)	1728(51.37)	3921(48.92)	608(48.92)	789(45.22)	
Male	483(32.69)	1483(48.63)	3814(51.08)	777(51.08)	991(54.78)	
Race/ethnicity, %						<0.001
Non-Hispanic White	657(70.46)	1159(62.34)	2886(64.89)	713(72.83)	918(72.65)	
Non-Hispanic Black	188(7.34)	686(12.58)	1672(11.54)	271(11.22)	407(12.03)	
Other race	612(22.20)	1366(25.08)	3177(23.57)	401(15.95)	455(15.32)	
Education level, %						<0.001
Below high school	194(9.48)	613(12.65)	1898(16.86)	470(25.14)	577(24.98)	
High school	258(16.68)	671(21.45)	1773(23.05)	369(29.35)	457(27.22)	
Above high school	1005(73.84)	1927(65.90)	4064(60.09)	546(45.50)	746(47.80)	
Family PIR, %						<0.001
≤1.0	271(12.78)	713(15.79)	1702(15.42)	306(16.63)	417(16.89)	
1.1–3.0	535(30.49)	1255(34.38)	3212(35.43)	685(47.18)	890(46.62)	
>3.0	651(56.74)	1243(49.83)	2821(49.15)	394(36.19)	473(36.49)	

Smoking status, %						<0.001
Never smoker	1004(65.82)	1980(60.01)	4372(55.25)	649(47.09)	729(39.83)	
Former smoker	185(15.70)	622(22.11)	1784(24.73)	544(40.90)	671(38.58)	
Current smoker	268(18.48)	609(17.88)	1579(20.02)	192(12.01)	380(21.60)	
Drinking status, %						<0.001
Nondrinker	185(9.86)	332(8.67)	1036(10.29)	265(18.90)	249(12.03)	
Former drinker	89(5.74)	251(7.36)	966(11.98)	337(23.05)	409(23.48)	
Current drinker	1183(84.40)	2628(83.97)	5733(77.73)	783(58.05)	1122(64.49)	
Physical activity, %						<0.001
Inactive	222(12.18)	569(16.28)	1915(21.59)	616(42.11)	742(37.13)	
Insufficiently active	470(31.79)	992(32.01)	2524(33.94)	397(29.85)	502(30.15)	
Active	765(56.02)	1650(51.70)	3296(44.46)	372(28.04)	536(32.72)	
Total energy intakes, kcal/day	1974.00 (1551.00, 2624.00)	2098.00 (1588.00, 2751.00)	2066.00 (1531.00, 2709.00)	1666.00 (1263.00, 2147.00)	1810.00 (1330.00, 2360.00)	<0.001
Serum calcium, mmol/L	2.35(2.30,2.40)	2.33(2.28,2.38)	2.33(2.28,2.40)	2.35(2.28,2.40)	2.33(2.28,2.40)	<0.001
Serum phosphorus, mmol/L	1.23(1.13,1.32)	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.07,1.29)	<0.001
Urinary creatinine, mg/dL	102.00 (57.00,160.00)	118.00 (69.00,176.00)	115.00 (69.00,170.00)	99.00 (65.00,143.00)	108.00 (67.00,155.00)	<0.001
Fasting blood glucose, mg/dL	91.00(86.00,95.00)	98.00(92.00,103.00)	103.00(96.00,112.00)	114.00(100.00,134.00)	108.00(98.00,126.00)	<0.001
Hemoglobin A1c, %	5.200(5.00,5.300)	5.300(5.100,5.600)	5.500(5.300,5.800)	6.00(5.600,6.600)	5.800(5.500,6.400)	<0.001
LDL-cholesterol, mg/dL	97.00(79.00,118.00)	112.00(92.00, 134.00)	118.00(96.00,142.00)	104.00(80.00,126.00)	94.00(74.00,121.00)	<0.001
HDL-cholesterol, mg/dL	62.00(53.00,73.00)	55.00(47.00,65.00)	48.00(40.00,59.00)	50.00(42.00,61.00)	48.00(40.00,59.00)	<0.001
Kidney stone, %						<0.001
No	1390(94.90)	3014(93.29)	6968(89.47)	1198(85.00)	1497(83.45)	
Yes	67(5.10)	197(6.71)	767(10.53)	187(15.00)	283(16.55)	

Abbreviations: PIR, poverty income ratio; LDL, low density lipoprotein; HDL, high density lipoprotein; CKM, cardiovascular-kidney-metabolic. Continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

Association between CKM syndrome stages and the prevalence of KS

Table 3 illustrates the ORs for KS prevalence across CKM syndrome stages. In the unadjusted model, KS likelihood rose progressively with advancing CKM stages, with Stage 4 showing almost 3.7 times the odds compared to Stage 0. This association remained robust in Model 1, which adjusted for age, sex, and race/ethnicity. The trend persisted in Model 2 with further adjustments for socioeconomic and lifestyle factors. In Model 3, even after additional adjustments for serum calcium, phosphorus, and creatinine, the ORs for KS prevalence continued to increase with CKM severity: 1.18 (95% CI: 0.83–1.68) for Stage 1, 1.72 (95% CI: 1.28–2.32) for Stage 2, 2.00 (95% CI: 1.29–3.10) for Stage 3, and 2.36 (95% CI: 1.64–3.40) for Stage 4. This indicates a significant and stepwise rise in KS prevalence with worsening CKM stages ($P_{trend} < 0.001$). To visually summarize the association between CKM syndrome stages and KS prevalence, the odds ratios (ORs) and 95% confidence intervals (CIs) from Table 3 are further illustrated in Figure 3 using a forest plot.

Table 3. OR (95% CIs) of the prevalence of kidney stone according to CKM syndrome stages among adults in NHANES 2007–2020.

	CKM syndrome stage					P_{trend}
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Crude	1.00 [Reference]	1.34(0.94,1.91)	2.19(1.64,2.93)	3.28(2.29,4.71)	3.69(2.68,5.09)	<0.001
Model 1	1.00 [Reference]	1.27(0.89,1.82)	1.84(1.37,2.48)	2.24(1.48,3.40)	2.63(1.87,3.72)	<0.001
Model 2	1.00 [Reference]	1.25(0.88,1.79)	1.80(1.34,2.42)	2.08(1.35,3.22)	2.45(1.71,3.51)	<0.001
Model 3	1.00 [Reference]	1.18(0.83,1.68)	1.72(1.28,2.32)	2.00(1.29,3.10)	2.36(1.64,3.40)	<0.001

Abbreviations: OR, Odd ratio; CI, confidence interval; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Model 1 was adjusted as age (20-39, 40-59, or ≥60), sex (male or female), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race); Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy

drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles); Model 3 was adjusted as model 2 plus serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles).

Stratified analysis

Table 4 presents stratified analyses of the association between CKM syndrome stage and KS prevalence. Among participants aged 20–59, Stage 4 was associated with over threefold increased odds of KS compared to Stage 0 (OR = 3.14, 95% CI: 2.08–4.73). In those aged ≥60 years, the association was weaker and nonsignificant (OR = 1.31, 95% CI: 0.45–3.80), with no significant age interaction (*P* for interaction = 0.482). Sex-stratified results were similar; in Stage 4, females and males had approximately 2.4 times the odds of KS, with no significant sex interaction (*P* for interaction = 0.299). Non-Hispanic Whites showed stronger associations (OR = 2.28, 95% CI: 1.45–3.60), with weaker trends in other ethnicities. Consistent patterns emerged across subgroups of family PIR, education level, smoking, drinking, and physical activity. Despite varying strengths, the association between CKM syndrome severity and KS prevalence remained consistent across these groups.

Table 4. Stratified analyses of the associations between CKM syndrome stage and the prevalence of kidney stone among adults in NHANES 2007–2020.

Subgroups	N	CKM syndrome stage					*P-int*
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Age, years							0.482
20-59	10216	1 [Reference]	1.35 (0.92-1.98)	2.10 (1.51-2.91)	2.79 (0.86-9.10)	3.14 (2.08-4.73)	
≥ 60	5352	1 [Reference]	0.61 (0.20-1.89)	0.96 (0.32-2.88)	1.15 (0.39-3.41)	1.31 (0.45-3.80)	
Sex, %							0.299
Female	8020	1 [Reference]	1.33 (0.85-2.07)	1.82 (1.21-2.74)	1.99 (1.05-3.77)	2.36 (1.40-4.00)	
Male	7548	1 [Reference]	1.09 (0.56-2.15)	1.78 (0.99-3.20)	2.09 (1.04-4.21)	2.47 (1.34-4.55)	
Race, %							0.351
Non-Hispanic White	6333	1 [Reference]	1.23 (0.79-1.92)	1.68 (1.16-2.43)	2.05 (1.17-3.57)	2.28 (1.45-3.60)	
Non-Hispanic Black	3224	1 [Reference]	0.79 (0.36-1.70)	1.50 (0.70-3.18)	1.94 (0.79-4.77)	1.53 (0.56-4.14)	
Other race	6011	1 [Reference]	1.10 (0.62-1.94)	1.91 (1.11-3.31)	1.66 (0.84-3.28)	3.02 (1.60-5.69)	
Family PIR, %							0.687
≤1.0	3409	1 [Reference]	1.75 (0.76-4.00)	2.42 (1.14-5.18)	3.02 (1.05-8.72)	4.37 (1.90-10.04)	
1.1–3.0	6577	1 [Reference]	1.34 (0.78-2.30)	1.84 (1.13-3.00)	1.94 (1.14-3.33)	2.56 (1.59-4.11)	
>3.0	5582	1	1.02 (0.62-	1.54 (1.00-	2.07 (1.13-	1.88 (1.05-	

		[Reference]	1.67)	2.39)	3.80)	3.37)	
Education level, %							0.571
Below high school	3752	1 [Reference]	1.72 (0.66-4.47)	3.10 (1.31-7.33)	2.78 (1.00-7.73)	4.34 (1.78-10.56)	
High school	3528	1 [Reference]	0.92 (0.41-2.07)	1.21 (0.59-2.49)	1.19 (0.47-3.03)	1.42 (0.67-3.01)	
Above high school	8288	1 [Reference]	1.22 (0.77-1.93)	1.75 (1.19-2.57)	2.53 (1.48-4.32)	2.47 (1.49-4.09)	
Smoking status, %							0.266
Nonsmokers	8734	1 [Reference]	1.47 (0.88-2.46)	2.29 (1.46-3.62)	2.40 (1.28-4.51)	3.61 (2.04-6.39)	
Former smokers	3806	1 [Reference]	0.84 (0.40-1.73)	1.17 (0.61-2.25)	1.73 (0.78-3.85)	1.63 (0.83-3.20)	
Current smokers	3028	1 [Reference]	0.93 (0.47-1.83)	1.23 (0.63-2.42)	1.23 (0.43-3.49)	1.41 (0.61-3.26)	
Drinking status, %							0.336
Nondrinker	2067	1 [Reference]	0.58 (0.20-1.74)	1.50 (0.73-3.11)	1.86 (0.66-5.24)	1.95 (0.84-4.52)	
Low-to-moderate drinker	2052	1 [Reference]	1.74 (0.51-5.94)	2.40 (0.87-6.66)	2.08 (0.63-6.81)	2.70 (0.82-8.91)	
Heavy drinker	11449	1 [Reference]	1.23 (0.82-1.87)	1.72 (1.21-2.43)	2.18 (1.31-3.63)	2.52 (1.63-3.88)	
Physical activity, %							0.575
Inactive	4064	1 [Reference]	1.19 (0.48-2.97)	1.47 (0.61-3.56)	1.49 (0.55-4.05)	2.24 (0.89-5.63)	
Insufficiently active	4885	1 [Reference]	1.00 (0.48-2.11)	2.06 (1.13-3.75)	2.86 (1.37-5.97)	2.69 (1.27-5.71)	
Active	6619	1 [Reference]	1.27 (0.81-1.99)	1.65 (1.10-2.49)	2.08 (1.15-3.78)	2.09 (1.24-3.51)	
Serum calcium, mmol/L							0.395
Quartile 1	4717	1 [Reference]	2.10 (1.06-4.16)	2.93 (1.59-5.41)	2.85 (1.22-6.65)	3.01 (1.35-6.70)	
Quartile 2	3638	1 [Reference]	1.20 (0.60-2.41)	1.66 (0.90-3.05)	2.01 (0.77-5.26)	3.05 (1.34-6.94)	
Quartile 3	3361	1 [Reference]	0.57 (0.29-1.11)	1.24 (0.71-2.17)	1.63 (0.75-3.58)	1.73 (0.80-3.72)	
Quartile 4	3852	1 [Reference]	1.24 (0.55-2.78)	1.59 (0.86-2.95)	1.98 (0.91-4.35)	2.41 (1.27-4.57)	
Serum phosphorus, mmol/L							0.408
Quartile 1	4635	1 [Reference]	1.16 (0.62-2.16)	1.52 (0.89-2.60)	1.52 (0.74-3.12)	2.23 (1.15-4.35)	
Quartile 2	3543	1 [Reference]	1.76 (0.67-4.63)	2.15 (0.82-5.65)	4.16 (1.27-13.63)	3.10 (1.00-9.60)	
Quartile 3	4131	1 [Reference]	1.48 (0.75-2.92)	2.28 (1.20-4.36)	2.24 (0.83-6.01)	3.20 (1.32-7.75)	
Quartile 4	3259	1 [Reference]	0.53 (0.26-1.08)	1.38 (0.77-2.48)	1.63 (0.72-3.69)	1.97 (1.02-3.83)	
Urinary creatinine, mg/dL							0.393
Quartile 1	3913	1 [Reference]	1.58 (0.76-3.28)	1.60 (0.85-3.03)	2.19 (0.95-5.07)	2.89 (1.31-6.39)	
Quartile 2	4038	1	1.04 (0.54-	1.35 (0.80-	1.69 (0.78-	2.06 (1.09-	

		[Reference]	1.98)	2.28)	3.66)	3.87)
Quartile 3	3750	1 [Reference]	1.83 (0.89-3.77)	2.85 (1.45-5.59)	2.85 (1.22-6.65)	3.12 (1.60-6.08)
Quartile 4	3867	1 [Reference]	0.68 (0.33-1.42)	1.43 (0.77-2.64)	1.80 (0.74-4.39)	1.69 (0.78-3.67)

Abbreviations: OR, Odd ratio; CI, confidence interval; PIR, poverty-to-income ratio; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Analyses were adjusted for age (20-39, 40-59, or ≥60), sex (male or female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race), education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles), serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles) when they were not the strata variables. *p-int*, p for interaction.

Discussion

This study explored the relationship between CKM syndrome stages and the prevalence of KS among 15,568 U.S. adults using data from the NHANES 2007–2020. We found that participants with CKM syndrome had significantly higher odds of KS as CKM stage advanced. Moreover, the association between the CKM syndrome stage and KS prevalence was consistent in the fully adjusted models.

Both CKM syndrome and KS are systemic conditions affecting multiple organs. This study shows KS prevalence is closely linked to advanced CKM syndrome, characterized by insulin resistance, obesity, dyslipidemia, and hypertension. These contribute to stone formation and reflect metabolic dysfunction. CKM syndrome begins early in life[15], inducing dysfunctional adipose tissue, inflammation, oxidative stress, and insulin resistance[16], leading to hypertension, hypertriglyceridemia, metabolic syndrome, and type 2 diabetes[7]. As these conditions progress, they burden the kidneys, causing CKD and worsening CKM syndrome[3].

Metabolic syndrome is a known risk factor for KS development. Type 2 diabetes patients have an elevated risk of urinary KS due to increased urinary oxalate excretion, enhancing calcium oxalate stone formation[17]. Their urinary profiles—high oxalate excretion and low pH—make them more prone to uric acid and calcium oxalate stones[17]. Uric acid stone formers face a higher risk of diabetes and glucose intolerance than non-stone formers[18];increasing HbA1c levels correlate with lower urinary pH, further contributing to KS risk[19].

Obesity is another significant factor associated with KS. Excess caloric intake results in greater

metabolic waste and altered urinary composition[20]. Studies show that waist circumference and body mass index are linked to higher KS risk among adults over 46 years of age[21]. In obese individuals, insulin resistance impairs renal ammonium excretion[9],and obesity induces a pro-inflammatory state contributing to KS via oxidative stress and altered renal function. Dyslipidemia is also linked to KS, particularly uric acid stone formation[22]. Masterson et al. found individuals with dyslipidemia are over twice as likely to develop KS[23], and Inci et al. reported that KS formers have significantly higher serum lipid levels[24].

A large longitudinal cohort study in Taiwan confirmed a strong relationship between metabolic syndrome and KS formation, with hypertension identified as the strongest predictor of metabolic syndrome components[25]. Metabolic dysfunction has been independently associated with a higher risk of KS, especially in individuals with both obesity and metabolic dysfunction[26]. A meta-analysis confirmed a positive correlation between the number of metabolic syndrome components (such as hypertension, obesity, and dyslipidemia) and risk of KS development[27]. In 694 aging males, Yung et al. found metabolic syndrome and particularly hypertension strongly associated with nephrolithiasis[28]. Kohjimoto et al. reported hypertension and dyslipidemia significantly linked to KS severity, while other metabolic traits showed less consistent associations [29]. While relationships between CKM syndrome components and KS vary across populations, our study found no significant demographic interactions, indicating a consistent association between CKM stages and KS prevalence across these groups.

KS and CKD are closely related, each potentially exacerbating the other. Stone formation can lead to long-term kidney damage, inducing CKD[28]. Patients with CKD often exhibit altered urinary excretion of calcium, oxalate, phosphate, and uric acid—key contributors to stone formation[30]. Impaired kidney function diminishes oxalate filtration and excretion, leading to its accumulation in the bloodstream[31]. The Chronic Renal Insufficiency Cohort study found that as estimated glomerular filtration rate (eGFR) declined in CKD stages 2–4, urinary oxalate excretion decreased[32], increasing stone risk due to metabolic imbalance. However, some studies suggest CKD may offer protection against KS[33]. One study observed that CKD patients with average creatinine clearance of 35–38 mL/min exhibited hypocitraturia without significant differences in other components[34]. since citrate inhibits calcium stone formation, this could influence stone risk. A single-center study indicated that urinary components involved in stone formation were positively associated with eGFR[35], implying that worse kidney function might reduce stone-forming constituents. Although current data suggest a connection, more comprehensive studies are needed to establish a clear pattern

of how worsening kidney function affects KS development.

Several large-scale epidemiological studies report that individuals with a history of KS have a higher risk of myocardial infarction, coronary heart disease, and stroke compared to those without stones[36,37]. Reiner's longitudinal study found that KS history is associated with greater carotid artery wall thickness[38]. His et al. identified a significant association between recurrent KS formation and coronary artery calcium (CAC), especially in those with higher CAC scores[39], suggesting a link between recurrent KS and increased coronary artery calcification. CVD-related metabolic factors such as cholesterol, phospholipids, and uric acid are associated with KS pathogenesis [40]. Evidence suggests that KS formers with CVD have lower renal alkali excretion and higher acid retention[41]. Hamono et al. found that CVD risk factors—including smoking, hypertension, and overweight—are positively correlated with calcium oxalate stone risk[42]. Abdominal aortic calcification significantly correlates with hypocitraturia; stone formers have notably lower urinary citrate excretion[43].These findings suggest that hypocitraturia may be a common mechanism for both CVD and KS.

CKM syndrome and increased prevalence of KS is particularly critical in the context of the COVID-19 pandemic, which has exacerbated the burden of CKM syndrome. Individuals with CKM syndrome are at higher risk of severe COVID-19 outcomes. A recent study of 81,051 individuals from a primary care database compared pre-pandemic (2017–2019) and pandemic (2020–2022) periods, revealing a significant increase in CKM syndrome components during the pandemic. Notably, prediabetes prevalence rose by 170%, while diabetes, hypertension, dyslipidemia, and obesity also showed marked increases. Nearly half of the patients exhibited at least one CKM component, underscoring the growing health burden and the urgent need for targeted interventions to address this escalating public health challenge[44].

Epidemiological data demonstrate that the progression of cardiovascular-kidney-metabolic (CKM) syndrome from stage 0 to stage 3 is associated with a significantly higher absolute risk of atherosclerotic CVD and heart failure, both of which remain leading causes of global morbidity and mortality[8]. Our findings further reveal a strong association between advancing CKM stages and increased KS prevalence, underscoring the systemic and interconnected nature of metabolic, cardiovascular, and kidney diseases. The COVID-19 pandemic has exacerbated the burden of CKM syndrome, amplifying its underlying mechanisms, including chronic inflammation, oxidative stress, and endothelial dysfunction, which collectively accelerate atherosclerosis and cardiovascular complications[45,46].

The association between CKM syndrome and KS prevalence involves several interconnected mechanisms. Patients with CKM syndrome are at higher risk of developing both calcium oxalate and uric acid stones, with urinary pH playing a critical role in stone composition; acidic urine promotes uric acid stones, while alkaline urine favors calcium phosphate stones. Insulin resistance impairs renal ammoniogenesis in proximal tubules, reducing ammonia production and lowering urinary pH[47], increasing uric acid stone risk. The inflammatory response also contributes to KS and CKM syndrome progression[48]; elevated urinary oxalate levels—a key risk factor for calcium oxalate stones—are influenced by inflammatory molecules like monocyte chemoattractant protein 1 and immune cell activity[48]. Both KS formation and atherosclerotic plaque development involve macrophage recruitment, releasing inflammatory mediators that cause tissue damage and calcium deposition[49]. Metabolic syndrome may also increase oxalate excretion[29]; elevated urinary oxalate harms renal parenchyma and may be reabsorbed into proximal tubules via passive diffusion[32]. The individual traits of CKM syndrome independently influence stone formation risk, and cumulatively further increase the risk of both calcium oxalate and uric acid stones. Future studies are needed to clarify these pathways and identify additional mechanisms.

Our study has several notable strengths, including its novel exploration of the relationship between CKM syndrome stages and KS prevalence, the use of a large, nationally representative sample from NHANES, and rigorous adjustment for multiple confounders to enhance the robustness of our findings. These strengths provide valuable insights into the systemic and interconnected nature of metabolic, cardiovascular, and kidney diseases. However, we fully acknowledge the limitations inherent in our study design. The cross-sectional nature of the analysis precludes the ability to infer causality or establish temporal relationships between CKM syndrome and KS development. Additionally, the reliance on self-reported KS history may introduce recall bias or misclassification, potentially affecting the accuracy of our results. While we adjusted for a wide range of covariates, the possibility of unmeasured confounders influencing the observed associations cannot be ruled out. Furthermore, the generalizability of our findings is limited to U.S. adults, and further research in diverse populations is needed to validate and extend these results.

Conclusions

This study demonstrates a clear and progressive association between advancing CKM syndrome stages and increased KS prevalence in a nationally representative U.S. adult population. Individuals with more advanced CKM stages are at higher risk of developing KS. These findings underscore the critical importance of early detection and effective management of CKM syndrome to mitigate KS risk and burden. Further research is needed to elucidate the underlying mechanisms driving this

association and to develop targeted prevention strategies for at-risk populations.

Figure legends

Figure 1: Flowchart of participant selection for the study.

Figure 2: Prevalence of kidney stones across CKM syndrome stages.

Abbreviations: CKM, cardiovascular-kidney-metabolic

Figure 3. Forest plot illustrating the odds ratios (ORs) and 95% confidence intervals (CIs) for kidney stone prevalence across CKM syndrome stages.

Abbreviations: OR, Odd ratio; CI, confidence interval; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Model 1 was adjusted as age (20-39, 40-59, or ≥60), sex (male or female), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race); Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles); Model 3 was adjusted as model 2 plus serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles).

Use of AI and AI-assisted technologies statement

AI has not been used in the writing process.

Author contributions

DW W: Conceived and designed the study; drafted the initial manuscript.

JJ T: Collected and analyzed the data and assisted in writing and editing the manuscript.

F S: Analyzed data and organized data.

DG Z: Supervised the research and was responsible for the manuscript revision and final approval.

GL L: Provided research resources; responsible for project management.

The guarantor of the study is DW W.; accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Abbreviations

CKM, cardiovascular-kidney-metabolic; KS, kidney stone; NHANES, National Health and Nutrition Examination Survey; ORs, odds ratio; CIs, confidence interval; AHA, American Heart Association; CVD, cardiovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; NCHS, National Center for Health Statistics; PIR, poverty-to-income ratio; PA, physical activity; IQRs, interquartile range.

Declaration

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Disclosure Statement

Shi Feng declare no competing interests and all other authors have no competing interest to declare.

Ethics Statement

All participants provided written informed consent and study procedures were approved by the National Center for Health Statistics Research Ethics Review Board (Protocol Number: Protocol #2011-17) and Ruijin Hospital(2024-177).

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Data Availability

NHANES data described in this manuscript are available at https://wwwn.cdc.gov/nchs/nhan

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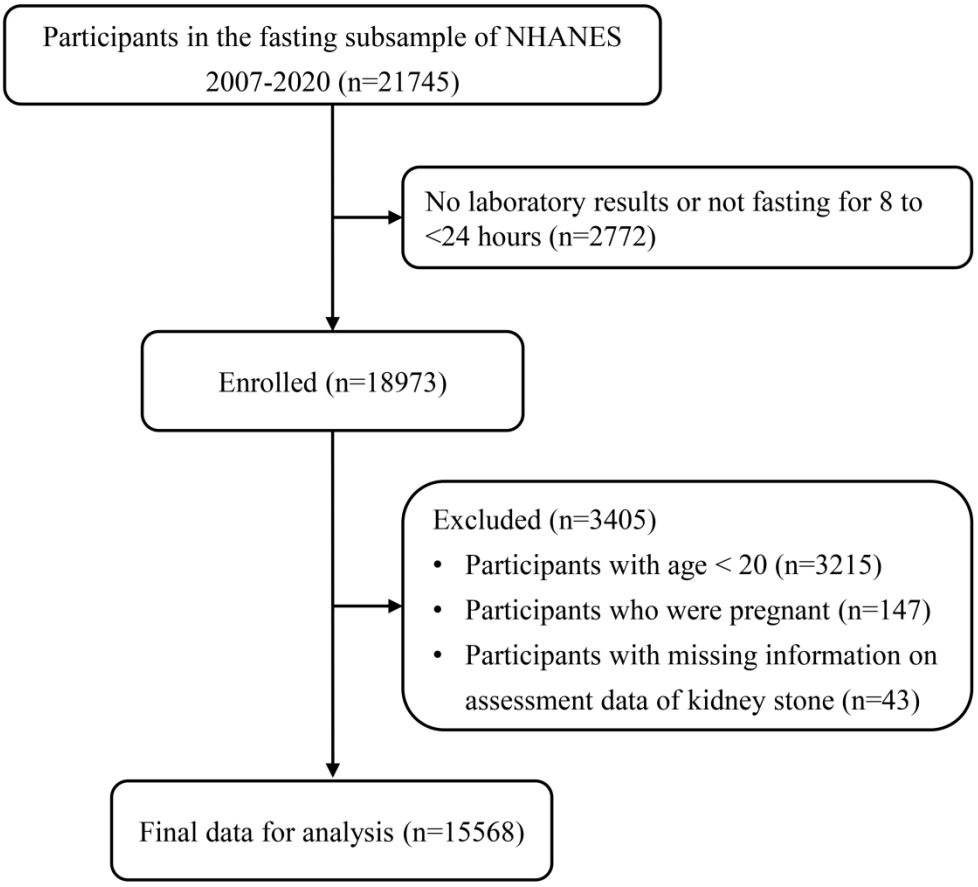

Figure 1: Flowchart of participant selection for the study.

146x132mm (600 x 600 DPI)

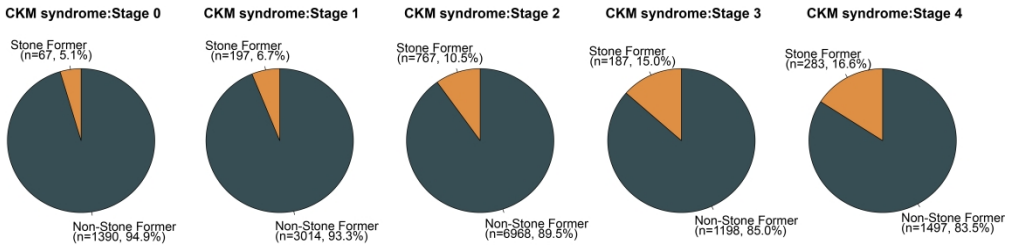

Figure 2: Prevalence of kidney stones across CKM syndrome stages.

508x121mm (300 x 300 DPI)

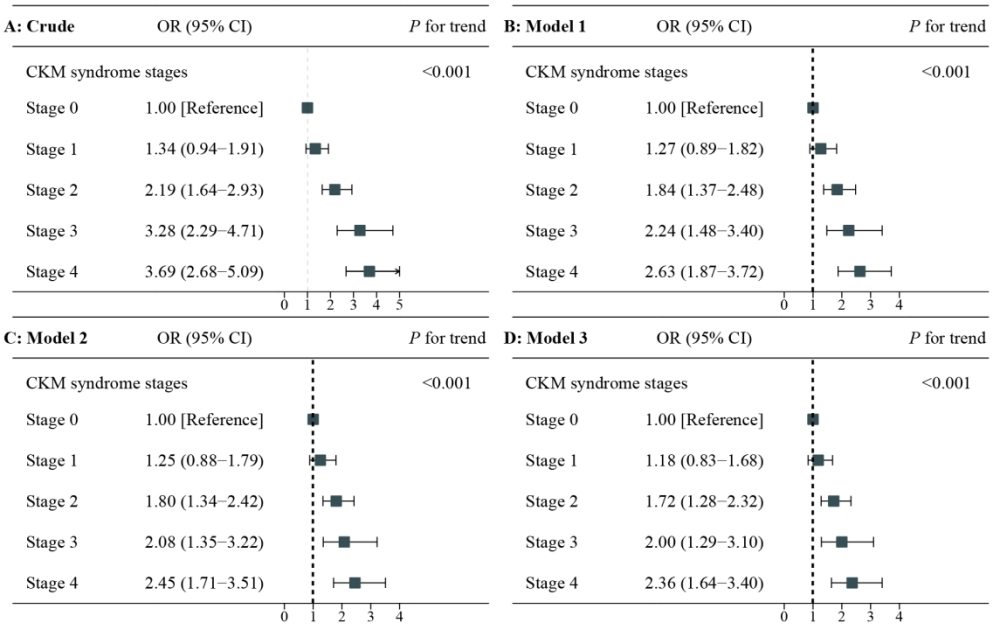

Figure 3. Forest plot illustrating the odds ratios (ORs) and 95% confidence intervals (CIs) for kidney stone prevalence across CKM syndrome stages.

159x99mm (300 x 300 DPI)

Online Supplementary Material

Association of Cardiovascular-Kidney-Metabolic Syndrome with Kidney Stones: A Population-based Study

Materials and methods

Assessment of cardiovascular-kidney-metabolic syndrome stages

Cardiovascular-kidney-metabolic (CKM) syndrome stages were classified using NHANES 2017-2018 data, in line with the 2023 AHA Presidential Advisory on CKM Health [1]. This classification system was specifically adapted to the NHANES dataset for this analysis. Definitions were adapted to the available data as follows:

CKM Stage 0: Participants with a normal BMI (<25 kg/m²), waist circumference (<88 cm for women, <102 cm for men), normoglycemia (fasting glucose <100 mg/dL, HbA1c <5.7%), normal blood pressure (systolic <130 mmHg, diastolic <80 mmHg), a healthy lipid profile (triglycerides <135 mg/dL), and no signs of CKD or cardiovascular disease (CVD).

CKM Stage 1: Individuals with an elevated BMI (≥25 kg/m²), increased waist circumference (≥88 cm for women, ≥102 cm for men), or prediabetes (HbA1c 5.7%-6.4% or fasting glucose 100-125 mg/dL), but without other metabolic risk factors or CKD.

CKM Stage 2: Participants with additional metabolic risk factors or moderate-to-high-risk CKD, as defined by KDIGO guidelines [2]. Risk factors included elevated triglycerides (≥135 mg/dL), hypertension, diabetes, or metabolic syndrome, characterized by at least three of the following:

increased waist circumference, low HDL (men <40 mg/dL, women <50 mg/dL), high triglycerides (≥150 mg/dL), elevated blood pressure (systolic ≥130 mmHg, diastolic ≥80 mmHg), or prediabetes.

CKM Stage 3: Those classified with very-high-risk CKD based on KDIGO criteria, or with a high 10-year CVD risk (≥20%), calculated using the AHA PREVENT risk equations (based on recommended thresholds [https://professional.heart.org/en/guidelines-and-statements/prevent-calculator]) [3].

CKM Stage 4: Individuals with self-reported established CVD, including coronary heart disease, angina, myocardial infarction, heart failure, or stroke. Data for atrial fibrillation and peripheral artery disease were unavailable and not included.

Assessment of Other Covariates

This study included several confounding variables such as family poverty-to-income ratio (PIR), drinking status, smoking status, physical activity, and total energy intake, which were defined as follows:

Family poverty income ratio Income was assessed using the poverty income ratio (PIR, the ratio of family income divided by a poverty threshold specific for family size using guidelines from the US Department of Health and Human Services) and categorized as ≤1.0, 1.1-3.0 and >3.0 [4].

Drinking status Drinking status was classified as nondrinker, low-to-moderate drinker (<2 drinks/day in men and <1 drink/day in women), or heavy drinker (≥2 drinks/day in men and ≥1 drinks/day in women) [5].

Smoking status Never smokers were classified as those who reported smoking <100 cigarettes during their lifetime. Those who smoked >100 cigarettes in their lifetime were considered as current smokers, and those who smoked >100 cigarettes and had quit smoking were considered as former smokers [5].

Physical activity Physical activity was categorized as inactive group (no leisure-time physical activity), insufficiently active group (leisure time moderate activity 1–5 times per week with MET ranging from 3 to 6 or leisure-time vigorous activity 1–3 times per week with MET >6), or active group (those who had more leisure-time moderate-or-vigorous activity than above) [6].

Dietary total energy intakes Dietary intake was assessed through two 24-hour recalls—one conducted in person at the NHANES Mobile Examination Center (MEC) and the second by telephone 3 to 10 days later. Participants reported all foods and beverages consumed during the 24-hour period, and total energy intake was estimated using the USDA Automated Multiple-Pass Method (AMPM) and analyzed via the Food and Nutrient Database for Dietary Studies (FNDDS). The average of the two recalls was used for analysis. Further details on dietary assessment can be found at: https://wwwn.cdc.gov/nchs/nhanes/tutorials/dietaryanalyses.aspx

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Association of Cardiovascular-Kidney-Metabolic Syndrome Stages with Kidney Stone Prevalence: A Population-based Analysis of NHANES 2007–2020

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*Guoliang Lu and Jinjun Tian contributed equally as co-correspondence authors.

Abstract

Background: The prevalence of kidney stones (KS) has been increasing globally, and their association with cardiovascular disease and metabolic syndrome suggests a shared underlying pathophysiology. However, the impact of different stages of cardiovascular-kidney-metabolic (CKM) syndrome on KS prevalence remains unclear.

Objective: This study aimed to investigate the association between the stages of cardiovascular-kidney-metabolic (CKM) syndrome and the prevalence of kidney stones (KS) in a nationally representative sample of adults in the United States.

Methods: A total of 15,568 participants aged ≥20 years were included in the National Health and Nutrition Examination Survey 2007–2020 fasting subsample. CKM syndrome stages (0–4) were defined based on the 2023 American Heart Association Presidential Advisory on CKM Health. The KS history was determined using self-reported data. Multivariable logistic regression models were used to assess the association between the CKM syndrome stage and KS prevalence.

Results: Of the 15,568 participants, 1,501 (9.64%) reported a history of KS. The KS prevalence increased progressively with advancing CKM stage, rising from 5.10% in stage 0 to 16.55% in stage 4 ($P < 0.001$). In the fully adjusted model, the odds ratios (ORs) for KS were 1.18 (95% confidence interval [CI]: 0.83–1.68) for Stage 1, 1.72 (95% CI: 1.28–2.32) for Stage 2, 2.00 (95% CI: 1.29–3.10) for Stage 3, and 2.36 (95% CI: 1.64–3.40) for Stage 4, compared to Stage 0 (P for trend < 0.001). Stratified analyses revealed no significant interactions between age, sex, race/ethnicity, or other subgroups.

Conclusion: This study demonstrated a significant stepwise increase in KS prevalence with the advancing stages of CKM syndrome. These findings highlight the importance of monitoring and managing CKM syndromes to mitigate the risks of KS.

Keywords: cardiovascular disease; kidney disease; metabolic syndrome; kidney stones; National Health and Nutrition Examination Survey.

Strengths and limitations of this study

Strengths:

- Utilized a nationally representative NHANES cohort (2007-2020) with complex survey weighting to ensure population generalizability.
- Implemented standardized 2023 AHA criteria for CKM syndrome staging, enhancing clinical consistency.
- Adjusted for comprehensive covariates including demographics, socioeconomic status, lifestyle factors, and biochemical markers.

Limitations:

- Kidney stone history was based on self-reported data, which may be subject to recall bias.
- The observational nature of the analysis precludes determination of temporal relationships.

Introduction

Kidney stones (KS) are hard mineral deposits forming in the renal calyces and pelvis when urine concentrations of substances like calcium, oxalate, uric acid, or phosphate become high enough to crystallize[1]. KS affects 10.1% of the U.S. population[2]. Recent research suggests KS is a systemic disorder linked to chronic diseases such as cardiovascular diseases (CVD), diabetes, and obesity, rather than being limited to the kidneys. Stone formation is a complex process influenced by genetic, metabolic, and environmental factors[3].

Cardiovascular-Kidney-Metabolic (CKM) syndrome, recently defined by the American Heart Association (AHA), represents a systemic disorder characterized by the pathophysiological interplay among metabolic risk factors (e.g., obesity, type 2 diabetes, hypertension, dyslipidemia, and insulin resistance), chronic kidney disease (CKD), and CVD[4]. These conditions share common underlying mechanisms, including systemic inflammation and metabolic dysfunction, which create a vicious cycle of organ damage and disease progression. The presence of one condition often exacerbates others, leading to increased risks of adverse outcomes, morbidity, and mortality[5–7]. CKM syndrome encompasses individuals at risk for CVD due to metabolic or kidney-related factors, as well as those with established CVD complicated by these conditions. Furthermore, social determinants of health, such as socioeconomic status and environmental factors, exacerbate biological risks and create barriers to effective lifestyle modification and care[8]. This integrated framework underscores the need for interdisciplinary approaches to address the complex mechanisms, clinical heterogeneity, and management challenges associated with CKM syndrome. In this study, we explore the association between CKM syndrome stages and KS prevalence, as both conditions are systemic and share underlying metabolic disturbances.

CKM syndrome comprises interconnected risk factors that elevate the likelihood of developing CVD, type 2 diabetes, and other health complications. Metabolic diseases such as obesity, diabetes mellitus (DM), and hypertension are associated with an increased risk of KS[9]. An 8-year follow-up study found a correlation between high blood pressure and KS development, with the risk further heightened when hypertension coexists with overweight conditions[10]. These factors can alter urine composition, metabolic processes, and kidney function, promoting stone formation. Specifically, increased acid excretion, low citrate levels, and high calcium excretion create a conducive environment for KS[11].

Emerging evidence supports the association between KS and various metabolic risk factors. Unhealthy metabolic status significantly increases KS risk, and combined effects can substantially elevate this risk. Previous studies have identified a broad range of KS risk factors, including biological

factors, high sodium intake, metabolic disturbances, and genetic predispositions[12]. Observational studies suggest that vascular calcification may also increase KS risk[13].A growing number of studies indicate a positive association between CVD and KS, suggesting potential shared pathological mechanisms. Therefore, each component of CKM syndrome may influence KS formation.

To better understand these connections, the American Heart Association (AHA) introduced a model classifying CKM syndrome into distinct stages[7]. Assessing the associations between the combined effects of these factors at various stages and KS prevalence is essential. However, few studies have explored the relationship between this new concept, CKM syndrome, and the KS stages. The aim of this study was to investigate the association between CKM syndrome stages and the prevalence of KS in a nationally representative sample of U.S. adults, utilizing data from the National Health and Nutrition Examination Survey (NHANES) from 2007 to 2020.

Materials and methods

Study population

NHANES is a nationally representative health and nutrition survey conducted by the National Center for Health Statistics (NCHS), with data collected through complex sampling methods (available at https://www.cdc.gov/nchs/nhanes). The study protocols were approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board (Protocols #2005-06, #2011-17, #2018-01) and Ruijin Hospital(2024-177), and all participants provided written informed consent.

Fasting samples were used to measure key biomarkers (glucose, lipids) essential for CKM syndrome staging. From the NHANES 2007–2020 fasting subsample (n = 21,745), we excluded 2,772 participants with missing laboratory data or insufficient fasting duration. Of the remaining 18,973 individuals, we further excluded 3,215 under 20 years old, 147 pregnant participants, and 43 with missing KS data, yielding a final sample of 15,568 for analysis (Figure 1).

Definition of KS

KS history was determined through self-reported data. Participants were classified as having a KS history if they affirmed a prior diagnosis of KS by a healthcare professional in response to the questionnaire item, “Have you/Has sample person (SP) ever had kidney stones?”. Additionally, recurrence of KS was defined as having experienced two or more episodes of passing kidney stones, based on the response to “How many times have you/has SP passed a kidney stone?”. This self-report method has been validated in prior studies, demonstrating a 97% accuracy rate in identifying clinically diagnosed KS cases [14].

Assessment of CKM Syndrome Stages

CKM syndrome stages (0–4) were classified according to the 2023 AHA Presidential Advisory on CKM Health[7], with adaptations for NHANES data. The stages were defined as follows: Stage 0: No CKM risk factors (e.g., absence of hypertension, hyperlipidemia, or metabolic abnormalities). Stage 1: Overweight, obesity, or dysfunctional adipose tissue without additional metabolic risk factors or CKD. Stage 2: Presence of metabolic risk factors (e.g., hypertension, dyslipidemia, insulin resistance) or CKD. Stage 3: High-risk CKD (e.g., eGFR <60 mL/min/1.73 m² or albuminuria ≥300 mg/g) or a high predicted 10-year CVD risk (≥20% based on validated risk scores). Stage 4: Established CVD (e.g., coronary artery disease, heart failure, or stroke). Detailed NHANES-adapted definitions for each stage, including specific criteria and thresholds, are provided in the Supplementary Material.

Assessment of Covariates

To account for potential confounding factors, the following covariates were included. Demographics: Age (categorized as 20–39, 40–59, ≥60 years), sex (male, female), and race/ethnicity (non-Hispanic white, non-Hispanic black, other). Socioeconomic Status: Education level (below high school, high school graduate, above high school) and family poverty-to-income ratio(PIR)(PIR ≤1.0, 1.1–3.0, >3.0). Lifestyle Factors: Drinking status: nondrinkers, low-to-moderate drinkers, or heavy drinkers (based on standard alcohol consumption thresholds); Smoking status: Never, former, or current smoker; Physical activity (PA): Classified as inactive, insufficiently active, or active based on self-reported adherence to physical activity guidelines. Biochemical and Nutritional Markers: Serum calcium, serum phosphorus, and urinary creatinine levels were divided into quartiles to account for metabolic variations; Total energy intake was assessed using 24-hour dietary recall data and categorized into quartiles. Detailed definitions and measurement protocols for all covariates are provided in the Supplementary Materials.

Statistical Analysis

All analyses adhered to NHANES guidelines, incorporating sample weights to account for the complex survey design, and were performed using the R "survey" package (version 4.3.2). Continuous variables were summarized as medians with interquartile ranges (IQR), while categorical variables were expressed as weighted percentages. Group comparisons were performed using the Mann-Whitney U test or Kruskal-Wallis H test for continuous variables with non-normal distributions and ordinal categorical variables, while the Chi-square test was applied to nominal categorical variables. Multivariable logistic regression models estimated the association between CKM stages and KS prevalence, adjusting for covariates, with results reported as odds ratios (ORs) and 95% confidence intervals (CIs). Subgroup analyses explored interactions between CKM stages and key variables (age,

sex, race/ethnicity, smoking status, and physical activity). A two-sided P <0.05 was considered statistically significant.

Patient and Public Involvement Statement

None

Results

Baseline Characteristics of Participants

Table 1 presents the survey-weighted baseline characteristics by KS status. Among 15,568 participants, 1,501 (9.64%) reported a history of KS. The median age was 48 years, with females comprising 51.32% of the cohort. Stone formers were significantly older; 38.12% were aged ≥60 years compared to 25.59% of non-stone formers ($P < 0.001$). Males had a higher prevalence of KS (53.27%) than females (46.73%) (P = 0.003). Participants with KS were more frequently classified into advanced CKM syndrome stages (Stages 3 and 4), with 24.42% versus 14.02% among non-stone formers ($P < 0.001$). Other covariates, including race/ethnicity, smoking status, drinking status, and physical activity, also showed significant differences between the groups.

Table 1. Survey-weighted characteristics of the general adult population by kidney stone in NHANES 2007–2020.

Characteristics	Overall	Non-Stone Former	Stone Former	*P* value
Participant, N	15568	14067	1501	
Age, years				<0.001
20-39	4893(35.91)	4618(37.40)	275(22.25)	
40-59	5323(37.27)	4799(37.01)	524(39.64)	
≥60	5352(26.82)	4650(25.59)	702(38.12)	
Sex, %				0.003
Female	8020(51.32)	7344(51.82)	676(46.73)	
Male	7548(48.68)	6723(48.18)	825(53.27)	
Race/ethnicity, %				<0.001
Non-Hispanic White	6333(66.13)	5553(65.19)	780(74.76)	
Non-Hispanic Black	3224(11.31)	3039(11.94)	185(5.54)	
Other race	6011(22.56)	5475(22.87)	536(19.70)	
Education level, %				0.604
Below high school	3752(16.24)	3382(16.18)	370(16.85)	
High school	3528(22.68)	3190(22.67)	338(22.74)	
Above high school	8288(61.08)	7495(61.15)	793(60.41)	
Family PIR, %				0.431
≤1.0	3409(15.40)	3092(15.53)	317(14.18)	
1.1–3.0	6577(36.32)	5943(36.28)	634(36.67)	
>3.0	5582(48.28)	5032(48.19)	550(49.15)	

Smoking status, %				0.018
Never smoker	8734(55.70)	7950(56.10)	784(52.09)	
Former smoker	3806(25.28)	3372(24.84)	434(29.31)	
Current smoker	3028(19.02)	2745(19.06)	283(18.60)	
Drinking status, %				0.002
Nondrinker	2067(10.53)	1867(10.44)	200(11.39)	
Former drinker	2052(11.88)	1800(11.41)	252(16.24)	
Current drinker	11449(77.59)	10400(78.16)	1049(72.37)	
Physical activity, %				<0.001
Inactive	4064(21.88)	3592(21.23)	472(27.81)	
Insufficiently active	4885(32.66)	4440(32.79)	445(31.45)	
Active	6619(45.46)	6035(45.98)	584(40.74)	
Total energy intakes, kcal/day	2007.00 (1495.00,2655.00)	2007.00 (1493.00,2667.00)	2005.00 (1541.00,2585.00)	0.679
Serum calcium, mmol/L	2.33(2.28,2.40)	2.33(2.28,2.40)	2.33(2.28,2.38)	0.029
Serum phosphorus, mmol/L	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.03,1.26)	<0.001
Urinary creatinine, mg/dL	114.00(67.00,168.00)	113.00(66.00,168.00)	120.00(77.00,168.00)	0.006
Fasting blood glucose, mg/dL	100.00(93.00,109.00)	100.00(93.00,109.00)	103.000(95.00,115.00)	<0.001
Hemoglobin A1c, %	5.50(5.20,5.80)	5.40(5.20,5.80)	5.600(5.30,6.10)	<0.001
LDL-cholesterol, mg/dL	111.00(89.00,135.00)	111.00(89.00,135.00)	113.00(91.000,135.00)	0.427
HDL- cholesterol, mg/dL	51.000(43.00,63.00)	52.00(43.00,63.00)	48.00(41.00,59.00)	<0.001
CKM syndrome stage, %				<0.001
Stage 0	1457(11.83)	1390(12.45)	67(6.15)	
Stage 1	3211(23.11)	3014(23.91)	197(15.78)	
Stage 2	7735(50.02)	6968(49.62)	767(53.65)	
Stage 3	1385(5.87)	1198(5.53)	187(8.96)	
Stage 4	1780(9.17)	1497(8.49)	283(15.46)	

Abbreviations: PIR, poverty income ratio; LDL, low density lipoprotein; HDL, high density lipoprotein; CKM, cardiovascular-kidney-metabolic. Continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

Table 2 summarizes the survey-weighted characteristics across CKM syndrome stages. In Stage 0, 66.05% of participants were aged 20–39 years, whereas in Stage 4, 69.49% were aged ≥60 years ($P < 0.001$). A higher proportion of males was observed in advanced stages: 54.78% in Stage 4 compared to 32.69% in Stage 0 ($P < 0.001$). KS prevalence increased consistently with advancing CKM stages, rising from 5.10% in Stage 0 to 16.55% in Stage 4. As shown in Figure 2, the prevalence

progressed as follows: 5.10% (Stage 0), 6.71% (Stage 1), 10.53% (Stage 2), 15.00% (Stage 3), and 16.55% (Stage 4), indicating a significant upward trend with increasing CKM syndrome severity ($P < 0.001$).

Table 2. Survey-weighted characteristics of the general adult population by CKM syndrome stages in NHANES 2007–2020.

Characteristics	CKM syndrome stage					*P* value
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Participant, N	1457	3211	7735	1385	1780	
Age, years						<0.001
20-39	996(66.05)	1676(53.78)	2138(30.22)	9(0.80)	74(5.53)	
40-59	382(28.56)	1134(35.22)	3345(46.34)	64(4.80)	398(24.98)	
≥60	79(5.39)	401(11.01)	2252(23.45)	1312(94.40)	1308(69.49)	
Sex, %						<0.001
Female	974(67.31)	1728(51.37)	3921(48.92)	608(48.92)	789(45.22)	
Male	483(32.69)	1483(48.63)	3814(51.08)	777(51.08)	991(54.78)	
Race/ethnicity, %						<0.001
Non-Hispanic White	657(70.46)	1159(62.34)	2886(64.89)	713(72.83)	918(72.65)	
Non-Hispanic Black	188(7.34)	686(12.58)	1672(11.54)	271(11.22)	407(12.03)	
Other race	612(22.20)	1366(25.08)	3177(23.57)	401(15.95)	455(15.32)	
Education level, %						<0.001
Below high school	194(9.48)	613(12.65)	1898(16.86)	470(25.14)	577(24.98)	
High school	258(16.68)	671(21.45)	1773(23.05)	369(29.35)	457(27.22)	
Above high school	1005(73.84)	1927(65.90)	4064(60.09)	546(45.50)	746(47.80)	
Family PIR, %						<0.001
≤1.0	271(12.78)	713(15.79)	1702(15.42)	306(16.63)	417(16.89)	
1.1–3.0	535(30.49)	1255(34.38)	3212(35.43)	685(47.18)	890(46.62)	
>3.0	651(56.74)	1243(49.83)	2821(49.15)	394(36.19)	473(36.49)	
Smoking status, %						<0.001
Never smoker	1004(65.82)	1980(60.01)	4372(55.25)	649(47.09)	729(39.83)	
Former smoker	185(15.70)	622(22.11)	1784(24.73)	544(40.90)	671(38.58)	
Current smoker	268(18.48)	609(17.88)	1579(20.02)	192(12.01)	380(21.60)	

Drinking status, %						<0.001
Nondrinker	185(9.86)	332(8.67)	1036(10.29)	265(18.90)	249(12.03)	
Former drinker	89(5.74)	251(7.36)	966(11.98)	337(23.05)	409(23.48)	
Current drinker	1183(84.40)	2628(83.97)	5733(77.73)	783(58.05)	1122(64.49)	
Physical activity, %						<0.001
Inactive	222(12.18)	569(16.28)	1915(21.59)	616(42.11)	742(37.13)	
Insufficiently active	470(31.79)	992(32.01)	2524(33.94)	397(29.85)	502(30.15)	
Active	765(56.02)	1650(51.70)	3296(44.46)	372(28.04)	536(32.72)	
Total energy intakes, kcal/day	1974.00 (1551.00, 2624.00)	2098.00 (1588.00, 2751.00)	2066.00 (1531.00, 2709.00)	1666.00 (1263.00, 2147.00)	1810.00 (1330.00, 2360.00)	<0.001
Serum calcium, mmol/L	2.35(2.30,2.40)	2.33(2.28,2.38)	2.33(2.28,2.40)	2.35(2.28,2.40)	2.33(2.28,2.40)	<0.001
Serum phosphorus, mmol/L	1.23(1.13,1.32)	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.07,1.29)	1.16(1.07,1.29)	<0.001
Urinary creatinine, mg/dL	102.00 (57.00,160.00)	118.00 (69.00,176.00)	115.00 (69.00,170.00)	99.00 (65.00,143.00)	108.00 (67.00,155.00)	<0.001
Fasting blood glucose, mg/dL	91.00(86.00,95.00)	98.00(92.00,103.00)	103.00(96.00,112.00)	114.00(100.00,134.00)	108.00(98.00,126.00)	<0.001
Hemoglobin A1c, %	5.200(5.00,5.300)	5.300(5.100,5.600)	5.500(5.300,5.800)	6.00(5.600,6.600)	5.800(5.500,6.400)	<0.001
LDL-cholesterol, mg/dL	97.00(79.00,118.00)	112.00(92.00, 134.00)	118.00(96.00,142.00)	104.00(80.00,126.00)	94.00(74.00,121.00)	<0.001
HDL-cholesterol, mg/dL	62.00(53.00,73.00)	55.00(47.00,65.00)	48.00(40.00,59.00)	50.00(42.00,61.00)	48.00(40.00,59.00)	<0.001
Kidney stone, %						<0.001
No	1390(94.90)	3014(93.29)	6968(89.47)	1198(85.00)	1497(83.45)	
Yes	67(5.10)	197(6.71)	767(10.53)	187(15.00)	283(16.55)	

Abbreviations: PIR, poverty income ratio; LDL, low density lipoprotein; HDL, high density lipoprotein; CKM, cardiovascular-kidney-metabolic. Continuous variables without a normal distribution are presented as medians [interquartile ranges]. Sampling weights were applied for calculation of demographic descriptive statistics; N reflect the study sample while percentages reflect the survey-weighted data.

Association between CKM syndrome stages and the prevalence of KS

Table 3 illustrates the ORs for KS prevalence across CKM syndrome stages. In the unadjusted model, KS likelihood rose progressively with advancing CKM stages, with Stage 4 showing almost 3.7 times the odds compared to Stage 0. This association remained robust in Model 1, which adjusted for age, sex, and race/ethnicity. The trend persisted in Model 2 with further adjustments for socioeconomic and lifestyle factors. In Model 3, even after additional adjustments for serum calcium, phosphorus, and creatinine, the ORs for KS prevalence continued to increase with CKM severity: 1.18 (95% CI: 0.83–1.68) for Stage 1, 1.72 (95% CI: 1.28–2.32) for Stage 2, 2.00 (95% CI: 1.29–3.10) for Stage 3, and 2.36 (95% CI: 1.64–3.40) for Stage 4. This indicates a significant and stepwise rise in KS prevalence with worsening CKM stages ($P_{trend} < 0.001$). To visually summarize the association between CKM syndrome stages and KS prevalence, the odds ratios (ORs) and 95% confidence intervals (CIs) from Table 3 are further illustrated in Figure 3 using a forest plot.

Table 3. OR (95% CIs) of the prevalence of kidney stone according to CKM syndrome stages among adults in NHANES 2007–2020.

	CKM syndrome stage					P_{trend}
	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Crude	1.00 [Reference]	1.34(0.94,1.91)	2.19(1.64,2.93)	3.28(2.29,4.71)	3.69(2.68,5.09)	<0.001
Model 1	1.00 [Reference]	1.27(0.89,1.82)	1.84(1.37,2.48)	2.24(1.48,3.40)	2.63(1.87,3.72)	<0.001
Model 2	1.00 [Reference]	1.25(0.88,1.79)	1.80(1.34,2.42)	2.08(1.35,3.22)	2.45(1.71,3.51)	<0.001
Model 3	1.00 [Reference]	1.18(0.83,1.68)	1.72(1.28,2.32)	2.00(1.29,3.10)	2.36(1.64,3.40)	<0.001

Abbreviations: OR, Odd ratio; CI, confidence interval; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Model 1 was adjusted as age (20-39, 40-59, or ≥60), sex (male or female), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race); Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles); Model 3 was adjusted as model 2 plus serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles).

Stratified analysis

Table 4 presents stratified analyses of the association between CKM syndrome stage and KS

prevalence. Among participants aged 20–59, Stage 4 was associated with over threefold increased odds of KS compared to Stage 0 (OR = 3.14, 95% CI: 2.08–4.73). In those aged ≥60 years, the association was weaker and nonsignificant (OR = 1.31, 95% CI: 0.45–3.80), with no significant age interaction (*P* for interaction = 0.482). Sex-stratified results were similar; in Stage 4, females and males had approximately 2.4 times the odds of KS, with no significant sex interaction (*P* for interaction = 0.299). Non-Hispanic Whites showed stronger associations (OR = 2.28, 95% CI: 1.45–3.60), with weaker trends in other ethnicities. Consistent patterns emerged across subgroups of family PIR, education level, smoking, drinking, and physical activity. Despite varying strengths, the association between CKM syndrome severity and KS prevalence remained consistent across these groups.

Table 4. Stratified analyses of the associations between CKM syndrome stage and the prevalence of kidney stone among adults in NHANES 2007–2020.

Subgroups	N	CKM syndrome stage					*P-int*
		Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	
Age, years							0.482
20-59	10216	1 [Reference]	1.35 (0.92-1.98)	2.10 (1.51-2.91)	2.79 (0.86-9.10)	3.14 (2.08-4.73)	
≥ 60	5352	1 [Reference]	0.61 (0.20-1.89)	0.96 (0.32-2.88)	1.15 (0.39-3.41)	1.31 (0.45-3.80)	
Sex, %							0.299
Female	8020	1 [Reference]	1.33 (0.85-2.07)	1.82 (1.21-2.74)	1.99 (1.05-3.77)	2.36 (1.40-4.00)	
Male	7548	1 [Reference]	1.09 (0.56-2.15)	1.78 (0.99-3.20)	2.09 (1.04-4.21)	2.47 (1.34-4.55)	
Race, %							0.351
Non-Hispanic White	6333	1 [Reference]	1.23 (0.79-1.92)	1.68 (1.16-2.43)	2.05 (1.17-3.57)	2.28 (1.45-3.60)	
Non-Hispanic Black	3224	1 [Reference]	0.79 (0.36-1.70)	1.50 (0.70-3.18)	1.94 (0.79-4.77)	1.53 (0.56-4.14)	
Other race	6011	1 [Reference]	1.10 (0.62-1.94)	1.91 (1.11-3.31)	1.66 (0.84-3.28)	3.02 (1.60-5.69)	
Family PIR, %							0.687
≤1.0	3409	1 [Reference]	1.75 (0.76-4.00)	2.42 (1.14-5.18)	3.02 (1.05-8.72)	4.37 (1.90-10.04)	
1.1–3.0	6577	1 [Reference]	1.34 (0.78-2.30)	1.84 (1.13-3.00)	1.94 (1.14-3.33)	2.56 (1.59-4.11)	
>3.0	5582	1 [Reference]	1.02 (0.62-1.67)	1.54 (1.00-2.39)	2.07 (1.13-3.80)	1.88 (1.05-3.37)	
Education level, %							0.571
Below high school	3752	1 [Reference]	1.72 (0.66-4.47)	3.10 (1.31-7.33)	2.78 (1.00-7.73)	4.34 (1.78-10.56)	
High school	3528	1 [Reference]	0.92 (0.41-2.07)	1.21 (0.59-2.49)	1.19 (0.47-3.03)	1.42 (0.67-3.01)	
Above high school	8288	1 [Reference]	1.22 (0.77-1.93)	1.75 (1.19-2.57)	2.53 (1.48-4.32)	2.47 (1.49-4.09)	
Smoking status, %							0.266
Nonsmokers	8734	1 [Reference]	1.47 (0.88-2.46)	2.29 (1.46-3.62)	2.40 (1.28-4.51)	3.61 (2.04-6.39)	
Former smokers	3806	1	0.84 (0.40-	1.17 (0.61-	1.73 (0.78-	1.63 (0.83-	

		[Reference]	1.73)	2.25)	3.85)	3.20)
Current smokers	3028	1 [Reference]	0.93 (0.47-1.83)	1.23 (0.63-2.42)	1.23 (0.43-3.49)	1.41 (0.61-3.26)
Drinking status, %						0.336
Nondrinker	2067	1 [Reference]	0.58 (0.20-1.74)	1.50 (0.73-3.11)	1.86 (0.66-5.24)	1.95 (0.84-4.52)
Low-to-moderate drinker	2052	1 [Reference]	1.74 (0.51-5.94)	2.40 (0.87-6.66)	2.08 (0.63-6.81)	2.70 (0.82-8.91)
Heavy drinker	11449	1 [Reference]	1.23 (0.82-1.87)	1.72 (1.21-2.43)	2.18 (1.31-3.63)	2.52 (1.63-3.88)
Physical activity, %						0.575
Inactive	4064	1 [Reference]	1.19 (0.48-2.97)	1.47 (0.61-3.56)	1.49 (0.55-4.05)	2.24 (0.89-5.63)
Insufficiently active	4885	1 [Reference]	1.00 (0.48-2.11)	2.06 (1.13-3.75)	2.86 (1.37-5.97)	2.69 (1.27-5.71)
Active	6619	1 [Reference]	1.27 (0.81-1.99)	1.65 (1.10-2.49)	2.08 (1.15-3.78)	2.09 (1.24-3.51)
Serum calcium, mmol/L						0.395
Quartile 1	4717	1 [Reference]	2.10 (1.06-4.16)	2.93 (1.59-5.41)	2.85 (1.22-6.65)	3.01 (1.35-6.70)
Quartile 2	3638	1 [Reference]	1.20 (0.60-2.41)	1.66 (0.90-3.05)	2.01 (0.77-5.26)	3.05 (1.34-6.94)
Quartile 3	3361	1 [Reference]	0.57 (0.29-1.11)	1.24 (0.71-2.17)	1.63 (0.75-3.58)	1.73 (0.80-3.72)
Quartile 4	3852	1 [Reference]	1.24 (0.55-2.78)	1.59 (0.86-2.95)	1.98 (0.91-4.35)	2.41 (1.27-4.57)
Serum phosphorus, mmol/L						0.408
Quartile 1	4635	1 [Reference]	1.16 (0.62-2.16)	1.52 (0.89-2.60)	1.52 (0.74-3.12)	2.23 (1.15-4.35)
Quartile 2	3543	1 [Reference]	1.76 (0.67-4.63)	2.15 (0.82-5.65)	4.16 (1.27-13.63)	3.10 (1.00-9.60)
Quartile 3	4131	1 [Reference]	1.48 (0.75-2.92)	2.28 (1.20-4.36)	2.24 (0.83-6.01)	3.20 (1.32-7.75)
Quartile 4	3259	1 [Reference]	0.53 (0.26-1.08)	1.38 (0.77-2.48)	1.63 (0.72-3.69)	1.97 (1.02-3.83)
Urinary creatinine, mg/dL						0.393
Quartile 1	3913	1 [Reference]	1.58 (0.76-3.28)	1.60 (0.85-3.03)	2.19 (0.95-5.07)	2.89 (1.31-6.39)
Quartile 2	4038	1 [Reference]	1.04 (0.54-1.98)	1.35 (0.80-2.28)	1.69 (0.78-3.66)	2.06 (1.09-3.87)
Quartile 3	3750	1 [Reference]	1.83 (0.89-3.77)	2.85 (1.45-5.59)	2.85 (1.22-6.65)	3.12 (1.60-6.08)
Quartile 4	3867	1 [Reference]	0.68 (0.33-1.42)	1.43 (0.77-2.64)	1.80 (0.74-4.39)	1.69 (0.78-3.67)

Abbreviations: OR, Odd ratio; CI, confidence interval; PIR, poverty-to-income ratio; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Analyses were adjusted for age (20-39, 40-59, or ≥60), sex (male or female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race), education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in

quartiles), serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles) when they were not the strata variables. *p-int*, p for interaction.

Discussion

This study explored the relationship between CKM syndrome stages and the prevalence of KS among 15,568 U.S. adults using data from the NHANES 2007–2020. We found that participants with CKM syndrome had significantly higher odds of KS as CKM stage advanced. Moreover, the association between the CKM syndrome stage and KS prevalence was consistent in the fully adjusted models.

Both CKM syndrome and KS are systemic conditions affecting multiple organs. This study shows KS prevalence is closely linked to advanced CKM syndrome, characterized by insulin resistance, obesity, dyslipidemia, and hypertension. These contribute to stone formation and reflect metabolic dysfunction. CKM syndrome begins early in life[15], inducing dysfunctional adipose tissue, inflammation, oxidative stress, and insulin resistance[16], leading to hypertension, hypertriglyceridemia, metabolic syndrome, and type 2 diabetes[7]. As these conditions progress, they burden the kidneys, causing CKD and worsening CKM syndrome[3].

Metabolic syndrome is a known risk factor for KS development. Type 2 diabetes patients have an elevated risk of urinary KS due to increased urinary oxalate excretion, enhancing calcium oxalate stone formation[17]. Their urinary profiles—high oxalate excretion and low pH—make them more prone to uric acid and calcium oxalate stones[17]. Uric acid stone formers face a higher risk of diabetes and glucose intolerance than non-stone formers[18];increasing HbA1c levels correlate with lower urinary pH, further contributing to KS risk[19].

Obesity is another significant factor associated with KS. Excess caloric intake results in greater metabolic waste and altered urinary composition[20]. Studies show that waist circumference and body mass index are linked to higher KS risk among adults over 46 years of age[21]. In obese individuals, insulin resistance impairs renal ammonium excretion[9],and obesity induces a pro-inflammatory state contributing to KS via oxidative stress and altered renal function. Dyslipidemia is also linked to KS, particularly uric acid stone formation[22]. Masterson et al. found individuals with dyslipidemia are over twice as likely to develop KS[23], and Inci et al. reported that KS formers have significantly higher serum lipid levels[24].

A large longitudinal cohort study in Taiwan confirmed a strong relationship between metabolic syndrome and KS formation, with hypertension identified as the strongest predictor of metabolic

syndrome components[25]. Metabolic dysfunction has been independently associated with a higher risk of KS, especially in individuals with both obesity and metabolic dysfunction[26]. A meta-analysis confirmed a positive correlation between the number of metabolic syndrome components (such as hypertension, obesity, and dyslipidemia) and risk of KS development[27]. In 694 aging males, Yung et al. found metabolic syndrome and particularly hypertension strongly associated with nephrolithiasis[28]. Kohjimoto et al. reported hypertension and dyslipidemia significantly linked to KS severity, while other metabolic traits showed less consistent associations [29]. While relationships between CKM syndrome components and KS vary across populations, our study found no significant demographic interactions, indicating a consistent association between CKM stages and KS prevalence across these groups.

KS and CKD are closely related, each potentially exacerbating the other. Stone formation can lead to long-term kidney damage, inducing CKD[28]. Patients with CKD often exhibit altered urinary excretion of calcium, oxalate, phosphate, and uric acid—key contributors to stone formation[30]. Impaired kidney function diminishes oxalate filtration and excretion, leading to its accumulation in the bloodstream[31]. The Chronic Renal Insufficiency Cohort study found that as estimated glomerular filtration rate (eGFR) declined in CKD stages 2–4, urinary oxalate excretion decreased[32], increasing stone risk due to metabolic imbalance. However, some studies suggest CKD may offer protection against KS[33]. One study observed that CKD patients with average creatinine clearance of 35–38 mL/min exhibited hypocitraturia without significant differences in other components[34]. since citrate inhibits calcium stone formation, this could influence stone risk. A single-center study indicated that urinary components involved in stone formation were positively associated with eGFR[35], implying that worse kidney function might reduce stone-forming constituents. Although current data suggest a connection, more comprehensive studies are needed to establish a clear pattern of how worsening kidney function affects KS development.

Several large-scale epidemiological studies report that individuals with a history of KS have a higher risk of myocardial infarction, coronary heart disease, and stroke compared to those without stones[36,37]. Reiner's longitudinal study found that KS history is associated with greater carotid artery wall thickness[38]. His et al. identified a significant association between recurrent KS formation and coronary artery calcium (CAC), especially in those with higher CAC scores[39], suggesting a link between recurrent KS and increased coronary artery calcification. CVD-related metabolic factors such as cholesterol, phospholipids, and uric acid are associated with KS pathogenesis [40]. Evidence suggests that KS formers with CVD have lower renal alkali excretion and higher acid retention[41]. Hamono et al. found that CVD risk factors—including smoking, hypertension, and overweight—are

positively correlated with calcium oxalate stone risk[42]. Abdominal aortic calcification significantly correlates with hypocitraturia; stone formers have notably lower urinary citrate excretion[43].These findings suggest that hypocitraturia may be a common mechanism for both CVD and KS.

CKM syndrome and increased prevalence of KS is particularly critical in the context of the COVID-19 pandemic, which has exacerbated the burden of CKM syndrome. Individuals with CKM syndrome are at higher risk of severe COVID-19 outcomes. A recent study of 81,051 individuals from a primary care database compared pre-pandemic (2017–2019) and pandemic (2020–2022) periods, revealing a significant increase in CKM syndrome components during the pandemic. Notably, prediabetes prevalence rose by 170%, while diabetes, hypertension, dyslipidemia, and obesity also showed marked increases. Nearly half of the patients exhibited at least one CKM component, underscoring the growing health burden and the urgent need for targeted interventions to address this escalating public health challenge[44].

Epidemiological data demonstrate that the progression of cardiovascular-kidney-metabolic (CKM) syndrome from stage 0 to stage 3 is associated with a significantly higher absolute risk of atherosclerotic CVD and heart failure, both of which remain leading causes of global morbidity and mortality[8]. Our findings further reveal a strong association between advancing CKM stages and increased KS prevalence, underscoring the systemic and interconnected nature of metabolic, cardiovascular, and kidney diseases. The COVID-19 pandemic has exacerbated the burden of CKM syndrome, amplifying its underlying mechanisms, including chronic inflammation, oxidative stress, and endothelial dysfunction, which collectively accelerate atherosclerosis and cardiovascular complications[45,46].

The association between CKM syndrome and KS prevalence involves several interconnected mechanisms. Patients with CKM syndrome are at higher risk of developing both calcium oxalate and uric acid stones, with urinary pH playing a critical role in stone composition; acidic urine promotes uric acid stones, while alkaline urine favors calcium phosphate stones. Insulin resistance impairs renal ammoniogenesis in proximal tubules, reducing ammonia production and lowering urinary pH[47], increasing uric acid stone risk. The inflammatory response also contributes to KS and CKM syndrome progression[48]; elevated urinary oxalate levels—a key risk factor for calcium oxalate stones—are influenced by inflammatory molecules like monocyte chemoattractant protein 1 and immune cell activity[48]. Both KS formation and atherosclerotic plaque development involve macrophage recruitment, releasing inflammatory mediators that cause tissue damage and calcium deposition[49]. Metabolic syndrome may also increase oxalate excretion[29]; elevated urinary oxalate harms renal parenchyma and may be reabsorbed into proximal tubules via passive diffusion[32]. The individual

traits of CKM syndrome independently influence stone formation risk, and cumulatively further increase the risk of both calcium oxalate and uric acid stones. Future studies are needed to clarify these pathways and identify additional mechanisms.

Our study has several notable strengths, including its novel exploration of the relationship between CKM syndrome stages and KS prevalence, the use of a large, nationally representative sample from NHANES, and rigorous adjustment for multiple confounders to enhance the robustness of our findings. These strengths provide valuable insights into the systemic and interconnected nature of metabolic, cardiovascular, and kidney diseases. However, we fully acknowledge the limitations inherent in our study design. The cross-sectional nature of the analysis precludes the ability to infer causality or establish temporal relationships between CKM syndrome and KS development. Additionally, the reliance on self-reported KS history may introduce recall bias or misclassification, potentially affecting the accuracy of our results. While we adjusted for a wide range of covariates, the possibility of unmeasured confounders influencing the observed associations cannot be ruled out. Furthermore, the generalizability of our findings is limited to U.S. adults, and further research in diverse populations is needed to validate and extend these results.

Conclusions

This study demonstrates a clear and progressive association between advancing CKM syndrome stages and increased KS prevalence in a nationally representative U.S. adult population. Individuals with more advanced CKM stages are at higher risk of developing KS. These findings underscore the critical importance of early detection and effective management of CKM syndrome to mitigate KS risk and burden. Further research is needed to elucidate the underlying mechanisms driving this association and to develop targeted prevention strategies for at-risk populations.

Use of AI and AI-assisted technologies statement

AI has not been used in the writing process.

Author contributions

DW W: Conceived and designed the study; drafted the initial manuscript.

JJ T: Collected and analyzed the data and assisted in writing and editing the manuscript.

F S: Analyzed data and organized data.

DG Z: Supervised the research and was responsible for the manuscript revision and final approval.

GL L: Provided research resources; responsible for project management.

The guarantor of the study is DW W.; accepts full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Abbreviations

CKM, cardiovascular-kidney-metabolic; KS, kidney stone; NHANES, National Health and Nutrition Examination Survey; ORs, odds ratio; CIs, confidence interval; AHA, American Heart Association; CVD, cardiovascular disease; DM, diabetes mellitus; CKD, chronic kidney disease; NCHS, National Center for Health Statistics; PIR, poverty-to-income ratio; PA, physical activity; IQRs, interquartile range.

Declaration

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Competing Interests Statement:

The authors declare that no financial or other conflicts of interest exist related to this work. The funder had no involvement in study design, data collection/analysis, decision to publish, or content preparation.

Ethics Statement

All participants provided written informed consent and study procedures were approved by the National Center for Health Statistics Research Ethics Review Board (Protocol Number: Protocol #2011-17) and Ruijin Hospital(2024-177).

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Data Availability

NHANES data described in this manuscript are available at https://wwwn.cdc.gov/nchs/nhan

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Figure legends

Figure 1: Flowchart of participant selection for the study.

Figure 2: Prevalence of kidney stones across CKM syndrome stages.

Abbreviations: CKM, cardiovascular-kidney-metabolic

Figure 3. Forest plot illustrating the odds ratios (ORs) and 95% confidence intervals (CIs) for kidney stone prevalence across CKM syndrome stages.

Abbreviations: OR, Odd ratio; CI, confidence interval; CKM, cardiovascular-kidney-metabolic.

Data are presented as OR (95% CI) unless indicated otherwise; Model 1 was adjusted as age (20-39, 40-59, or ≥60), sex (male or female), and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, or Other race); Model 2 was adjusted as model 1 plus education level (below high school, high school, or above high school), family PIR (≤1.0, 1.1–3.0, or >3.0), drinking status (nondrinker, low-to-moderate drinker, or heavy drinker), smoking status (never smoker, former smoker, or current smoker), physical activity (inactive, insufficiently active, or active), total energy intakes (in quartiles); Model 3 was adjusted as model 2 plus serum calcium (in quartiles), serum phosphorus (in quartiles), and urinary creatinine (in quartiles).

594

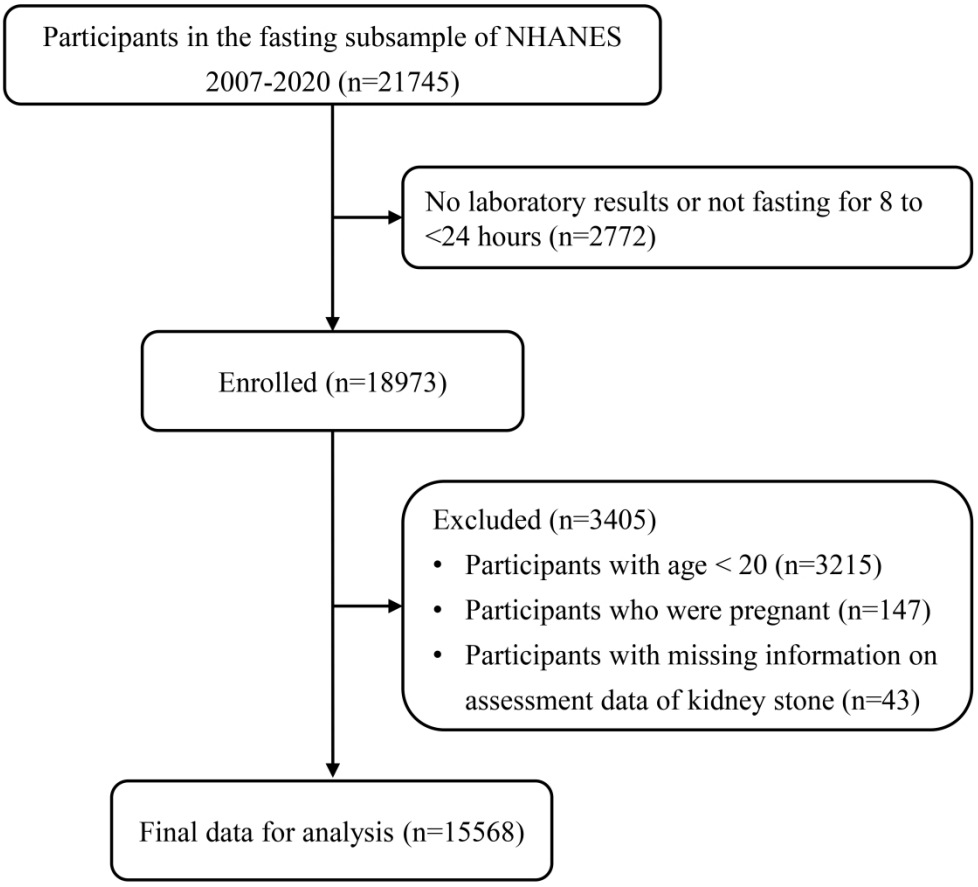

Figure 1: Flowchart of participant selection for the study.

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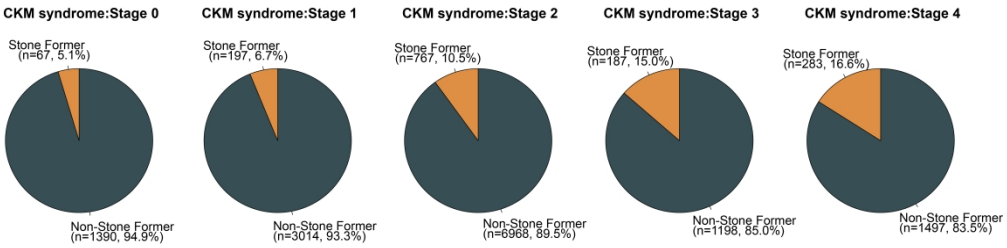

Figure 2: Prevalence of kidney stones across CKM syndrome stages.

508x121mm (300 x 300 DPI)

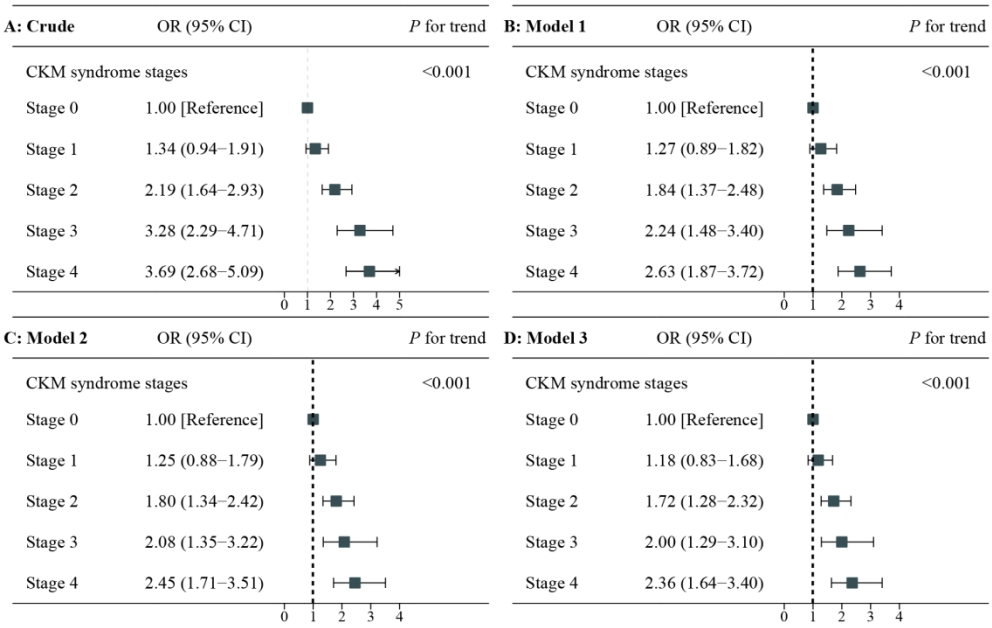

Figure 3. Forest plot illustrating the odds ratios (ORs) and 95% confidence intervals (CIs) for kidney stone prevalence across CKM syndrome stages.

159x99mm (300 x 300 DPI)

Online Supplementary Material

Association of Cardiovascular-Kidney-Metabolic Syndrome with Kidney Stones: A Population-based Study

Materials and methods

Assessment of cardiovascular-kidney-metabolic syndrome stages

Cardiovascular-kidney-metabolic (CKM) syndrome stages were classified using NHANES 2017-2018 data, in line with the 2023 AHA Presidential Advisory on CKM Health [1]. This classification system was specifically adapted to the NHANES dataset for this analysis. Definitions were adapted to the available data as follows:

CKM Stage 0: Participants with a normal BMI (<25 kg/m²), waist circumference (<88 cm for women, <102 cm for men), normoglycemia (fasting glucose <100 mg/dL, HbA1c <5.7%), normal blood pressure (systolic <130 mmHg, diastolic <80 mmHg), a healthy lipid profile (triglycerides <135 mg/dL), and no signs of CKD or cardiovascular disease (CVD).

CKM Stage 1: Individuals with an elevated BMI (≥25 kg/m²), increased waist circumference (≥88 cm for women, ≥102 cm for men), or prediabetes (HbA1c 5.7%-6.4% or fasting glucose 100-125 mg/dL), but without other metabolic risk factors or CKD.

CKM Stage 2: Participants with additional metabolic risk factors or moderate-to-high-risk CKD, as defined by KDIGO guidelines [2]. Risk factors included elevated triglycerides (≥135 mg/dL), hypertension, diabetes, or metabolic syndrome, characterized by at least three of the following:

increased waist circumference, low HDL (men <40 mg/dL, women <50 mg/dL), high triglycerides (≥150 mg/dL), elevated blood pressure (systolic ≥130 mmHg, diastolic ≥80 mmHg), or prediabetes.

CKM Stage 3: Those classified with very-high-risk CKD based on KDIGO criteria, or with a high 10-year CVD risk (≥20%), calculated using the AHA PREVENT risk equations (based on recommended thresholds [https://professional.heart.org/en/guidelines-and-statements/prevent-calculator]) [3].

CKM Stage 4: Individuals with self-reported established CVD, including coronary heart disease, angina, myocardial infarction, heart failure, or stroke. Data for atrial fibrillation and peripheral artery disease were unavailable and not included.

Assessment of Other Covariates

This study included several confounding variables such as family poverty-to-income ratio (PIR), drinking status, smoking status, physical activity, and total energy intake, which were defined as follows:

Family poverty income ratio Income was assessed using the poverty income ratio (PIR, the ratio of family income divided by a poverty threshold specific for family size using guidelines from the US Department of Health and Human Services) and categorized as ≤1.0, 1.1-3.0 and >3.0 [4].

Drinking status Drinking status was classified as nondrinker, low-to-moderate drinker (<2 drinks/day in men and <1 drink/day in women), or heavy drinker (≥2 drinks/day in men and ≥1 drinks/day in women) [5].

Smoking status Never smokers were classified as those who reported smoking <100 cigarettes during their lifetime. Those who smoked >100 cigarettes in their lifetime were considered as current smokers, and those who smoked >100 cigarettes and had quit smoking were considered as former smokers [5].

Physical activity Physical activity was categorized as inactive group (no leisure-time physical activity), insufficiently active group (leisure time moderate activity 1–5 times per week with MET ranging from 3 to 6 or leisure-time vigorous activity 1–3 times per week with MET >6), or active group (those who had more leisure-time moderate-or-vigorous activity than above) [6].

Dietary total energy intakes Dietary intake was assessed through two 24-hour recalls—one conducted in person at the NHANES Mobile Examination Center (MEC) and the second by telephone 3 to 10 days later. Participants reported all foods and beverages consumed during the 24-hour period, and total energy intake was estimated using the USDA Automated Multiple-Pass Method (AMPM) and analyzed via the Food and Nutrient Database for Dietary Studies (FNDDS). The average of the two recalls was used for analysis. Further details on dietary assessment can be found at: https://wwwn.cdc.gov/nchs/nhanes/tutorials/dietaryanalyses.aspx

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