Am J Clin Exp Urol 2026;14(4):86-96
www.ajceu.us /ISSN:2330-1910/AJCEU0173373

Original Article

Association between the Zhejiang University index and kidney stone risks in US adults: evidence from NHANES 2007-2018

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Received April 16, 2026; Accepted July 22, 2026; Epub August 15, 2026; Published August 30, 2026

Abstract: Background: Kidney stones carry a substantial population health burden and are demonstrated to be increasingly associated with metabolic dysregulation. We examined whether the Zhejiang University (ZJU) index, a composite metabolic parameter derived from routine clinical data, is associated with kidney stone history in US adults. Methods: We used National Health and Nutrition Examination Survey (NHANES) 2007-2018 to assess the association between the ZJU index and self-report kidney stone history among adults aged 20 years or older. We applied survey-weighted logistic regression models to examine the relationship between the ZJU index and kidney stone history. Non-linearity was assessed using flexible spline and segmented regression. Discrimination was evaluated using receiver operating characteristic analysis. Results: Among the 25,605 participants analyzed, 2,484 (9.7%) reported a history of kidney stones. Prevalence increased across ZJU index quartiles, from 4.09% in quartile 1 to 16.90% in quartile 4. In fully adjusted models, higher ZJU index was associated with higher odds of kidney stones (odds ratio 1.210, 95% CI: 1.186-1.234), with evidence of non-linearity and a turning point at 38.1. The ZJU index showed favorable discrimination (area under the curve 0.819) and an empirically derived threshold of 36.78 (sensitivity 76.2%, specificity 71.5%). Conclusion: Higher ZJU index was positively associated with kidney stone history in a nationally representative US sample, supporting its potential application in population-level risk stratification and prevention-oriented public health planning.

Keywords: Kidney stone, ZJU index, NHANES database, metabolic indicators, public health

Introduction

Kidney stone disease is a common urological condition and has shown a sustained increase in population burden over recent decades. In the United States, the prevalence of kidney stones in the adult population has been maintained at about 10% for a long time, and the incidence rate is higher in males compared to females [1-3]. Kidney stones can be classified into several types based on their chemical composition, including calcium oxalate, uric acid, struvite, and cystine stones [4]. Epidemiological data shows that multiple factors have the capability to potentially increase the likelihood of developing kidney stones. Among which, dietary habits, dehydration, obesity, and genetic predisposition are the most significant ones [5, 6]. Once a person has experienced an episode of kidney stones, the risk of recurrence is quite high. It is estimated that if preventive measures are not taken, there is a 50% chance of developing stones again within the next 15 years [6]. Researches have shown that the occurrence of kidney stones is closely related to various subclinical features of metabolic syndrome, such as obesity, high blood pressure (HBP) and dyslipidemia [7-9]. Therefore, kidney stones are considered as a systemic metabolic disease.

The Zhejiang University (ZJU) index, first proposed by Wang et al. [10] in 2015 as a risk factor for non-alcoholic fatty liver disease (NAFLD), is a novel metabolic parameter that takes consideration of alterations in multiple indicators,

https://doi.org/10.62347/PGCO5047

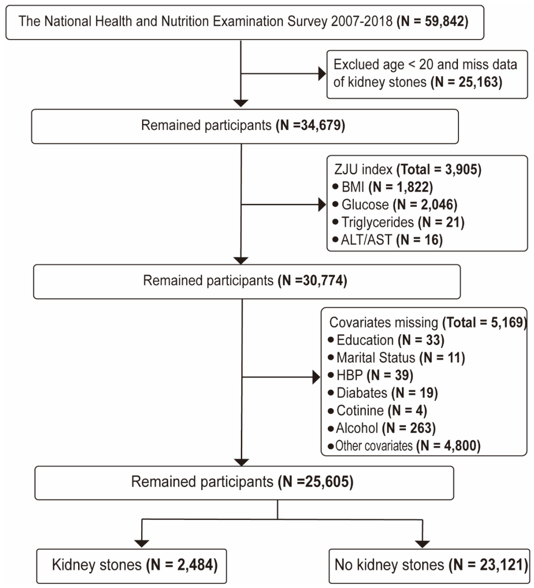

Figure 1. Flowchart of participant selection from the 2007-2018 National Health and Nutrition Examination Survey (NHANES). NHANES, National Health and Nutrition Examination Survey; ZJU, Zhejiang University; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBP, high blood pressure.

including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and fasting blood glucose (FBG). Compared to individual parameters included, the ZJU index provides a comprehensive perspective on metabolic health by encompassing these diverse factors, offering a more robust assessment of the risks of metabolic disorders and their associated disease [4, 5]. Recently, several studies have shown that the ZJU index is associated with a number of heath disorders including lipid regulation, insulin resistance and obesity [11, 12]. These metabolic abnormalities are biologically relevant to kidney stone formation. Dyslipidemia is associated with chronic inflammation and oxidative stress, while insulin resistance and obesity may increase urinary pH and promote urinary supersaturation, all of which may contribute to stone development [13, 14]. Of the components of the ZJU index, the rapid BMI growth trajectories during young adulthood were identified to be an independent risk factor of kidney stones [15]. Abnormal lipid levels may increase the risk of kidney stones through regulating metabolic pathways, and insulin sensitivity impairment, chronic inflammation, and oxidative stress activation might be the potential mechanisms [16-18]. Although evidences indicate that the ZJU index is closely related to kidney stones, very few light has been shed on the relationship between the ZJU index and kidney stone risks.

In this study, we analyzed data from the National Health and Nutrition Examination Survey (NHANES) to investigate the association between the ZJU index and self-reported kidney stone history and to evaluate the ability of the ZJU index to distinguish participants with and without a history of kidney stones.

Material and methods

Data and sample sources

The present study evaluated the data of six survey cycles from 2007 to 2018 in the NHANES database (https://wwwn.cdc.gov/nchs/nhanes/) to explore the association between the ZJU index and the prevalence of kidney stones. **Figure 1** illustrates the screening procedure of participants selection, and the exclusion criteria were as follows: 1) individuals younger than 20 years old and those with incomplete data on kidney stones (N = 25,163); 2) participants without ZJU index sub-parameter (N = 3,905), including BMI (N = 1,822), FBG (N = 2,046), TG (N = 21), and ALT/AST (N = 16); 3) participants who lack data for the basic covariates (n = 5,169), including education level (N = 33), marital status (N = 11), HBP (N = 39), diabetes (N = 19), cotinine (N = 4), and alcohol (N = 263).

Finally, 25,605 samples (2,484 cases of kidney stones and 23,121 non-stone controls) were included in this study. The ethical application of the NHANES database involving human subjects was approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board, and informed consents were obtained from all participants. In the conducting of this cross-sectional study, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed [19].

Definition of ZJU index

The ZJU index is a composite metric proposed by Wang et al. [10] in 2015 to predict the presence of NAFLD in the Chinese population. The formula used to calculate the ZJU index is defined as follows: ZJU index = 3 × ALT (IU/L)/AST (IU/L) + 2 (if females) + BMI (kg/m^2) + TG (mmol/L) + FBG (mmol/L).

The index integrates the ALT/AST ratio, BMI, triglycerides, fasting blood glucose, and sex into a single score, and was therefore used in this study as a composite indicator of metabolic burden [10].

Definition of kidney stones

The determination of a history of kidney stones depended on the question "(KIQ026) Have you/Has sample person (SP) ever had a kidney stone?" which is included in the questionnaire "Kidney Conditions - Urology" given to a population consisting of adults aged 20 and above. If the answer was "Yes", it was considered to have a history of kidney stones; if the answer was "No", it was considered as having no history of kidney stones; if the answer was "Don't known and refused", the corresponding participant was excluded.

Covariate assessment

Potential covariates were predetermined based on a comprehensive review of published literature [20, 21]. As shown in **Table 1**, these covariates included age, cotinine levels, gender, marital status, alcohol consumption, race/ethnicity, education level, as well as the presence of HBP and diabetes.

It's worth noting that cotinine was used to more accurately assess exposure to tobacco smoke [22, 23]. Alcohol consumption was classified into five categories: never, former, mild, moderate and heavy, defined as "<12 drinks in a lifetime", "≥12 drinks in one year but none in the past year, or ≥12 drinks in a lifetime but none in the past year", "≤1 drink/day for females and ≤2 drinks/day for males", "≤2 drinks/day for females and ≤3 drinks/day for males" and "≥3 drinks/day for females and ≥4 drinks/day for males", respectively [24].

Statistical analysis

In this study, R software version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) was utilized to conduct all statistical analyses. As required by the NCHS analysis guidelines, complex sampling design was adopted and sample weights were taken into consideration. The "survey" package was used to account for the complex sampling design of NHANES. For weight processing and regression analyses, survey R package was selected. All statistical tests were two-sided, and a *P* value <0.05 was considered to be statistically significant.

For comparison of baseline data in this study, continuous variables were presented as means ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages.

Baseline differences between participants with and without kidney stones were assessed using the Mann-Whitney U test for continuous variables and the chi-square test for categorical variables. Differences in kidney stone prevalence across ZJU index quartiles were assessed using the chi-square test. Association between the ZJU index and kidney stones prevalence was examined by three weighted multivariate logistic regression models, and odds ratios (OR), 95% confidence intervals (CI), and *P* values were used to determine the association. The ZJU index was analyzed both as a continuous variable and as quartiles, with the lowest quartile used as the reference group. Tests for trend were performed by modeling the ZJU index quartiles as an ordinal variable.

This study used crude model (unadjusted), model 1 (sex, age, race, educational level, and marital status were adjusted) and model 2 (model 1 + Cotinine, Alcohol drink, Diabetes and HBP were fully adjusted). The test for trend was used to analyze whether quantiles of the ZJU index (Q1-Q4) had a significant trend with increasing prevalence of kidney stones. RCS analysis was used to explore the nonlinear dose-response correlation between ZJU index and kidney stone formation. In the case of nonlinear correlations, a two-segment logistic regression model was used to fit each interval and determine threshold effects. Subgroup analyses were then performed to explore potential differences between subgroups. In addition, the discriminative ability of ZJU, BMI, TG, FBG, and ALT/AST was compared with ROC curves. The AUC of the ZJU index was compared with those of its individual components using paired DeLong tests. Finally, based on the principle of propensity score matching (PSM), vari-

Table 1. Baseline data of included participants

Characteristics	Overall	Non-stone controls	kidney stone patients	P
n	25605	23121	2484	
Age, (years)	49.90±17.64	49.23±17.67	56.10±16.10	<0.001
Gender, n (%)				<0.001
Female	13260 (51.8)	12170 (52.6)	1090 (43.9)	
Male	12345 (48.2)	10951 (47.4)	1394 (56.1)	
Race, n (%)				<0.001
Mexican American	4170 (16.3)	3845 (16.6)	325 (13.1)	
Non-Hispanic Black	5039 (19.7)	4729 (20.5)	310 (12.5)	
Non-Hispanic White	10752 (42.0)	9380 (40.6)	1372 (55.2)	
Other Hispanic	2713 (10.6)	2444 (10.6)	269 (10.8)	
Other Race - Including Multi-Racial	2931 (11.4)	2723 (11.8)	208 (8.4)	
Education, n (%)				0.003
Less Than 9th Grade	2762 (10.8)	2499 (10.8)	263 (10.6)	
9-11th Grade	3601 (14.1)	3245 (14.0)	356 (14.3)	
High School Grad	5917 (23.1)	5356 (23.2)	561 (22.6)	
Some College or AA degree	7530 (29.4)	6727 (29.1)	803 (32.3)	
College Graduate or above	5795 (22.6)	5294 (22.9)	501 (20.2)	
Marital Status, n (%)				<0.001
Divorced/Widowed	4836 (18.9)	4253 (18.4)	583 (23.5)	
Married/Living with partner	15416 (60.3)	13835 (59.9)	1581 (63.6)	
Never married/Separated	5353 (24.3)	5033 (21.8)	320 (12.9)	
BMI, (kg/m^2)	29.33±7.00	29.20±6.98	30.54±7.04	<0.001
HBP, n (%)				<0.001
No	16348 (63.8)	15121 (65.4)	1227 (49.4)	
Yes	9257 (36.2)	8000 (34.6)	1257 (50.6)	
Diabetes, n (%)				<0.001
No	21616 (84.4)	19775 (85.5)	1841 (74.1)	
Borderline	610 (2.4)	530 (2.3)	80 (3.2)	
Yes	3379 (13.2)	2816 (12.2)	563 (22.7)	
Cotinine, (ng/mL)	57.85±129.64	56.91±127.81	66.66±145.32	<0.001
Alcohol, n (%)				<0.001
Never	5088 (19.9)	4624 (20.0)	464 (18.7)	
Former	1257 (4.9)	1113 (4.8)	144 (5.8)	
Mild	9497 (37.1)	8465 (36.6)	1032 (41.5)	
Moderate	4417 (17.3)	4011 (17.3)	406 (16.3)	
Heavy	5346 (20.9)	4908 (21.2)	438 (17.6)	
ZJU index	40.72±8.64	40.28±8.49	44.83±8.94	<0.001

Data are presented as mean ± standard deviation (SD) or n (%). AA, associate degree; BMI, body mass index; HBP, high blood pressure.

ables including age, education, race, marital status, HBP, diabetes, and cotinine levels were selected as matching factors, and the control group was matched to the kidney stone group at a 2:1 ratio. Subsequently, the association between the ZJU index and kidney stones was reassessed using three weighted multivariate logistic regression models as sensitivity analysis.

Results

Clinical baseline features of subjects

This study incorporated a total of 25,605 participants, including 2,484 participants with kidney stones and 23,121 cases of non-stone controls. Baseline characteristics of these participants were summarized in **Table 1**. Between

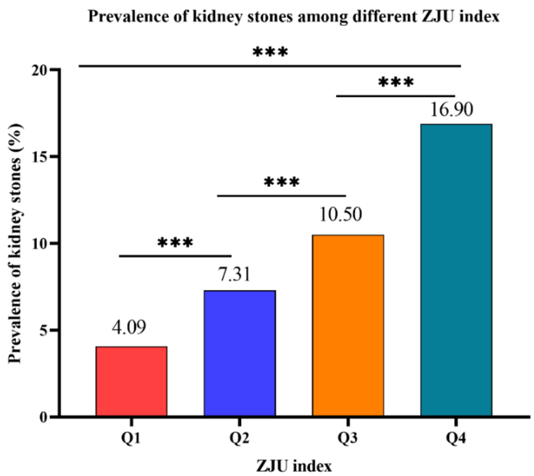

Figure 2. The prevalence of kidney stones across quartiles of ZJU index. ***P<0.001.

these two groups analyzed, age, gender, education, marital status, BMI, HBP, diabetes, smoking, alcohol consumption, and the ZJU index were statistically significantly different. We can observe that, apart from the higher ZJU index, participants with kidney stones were generally older, had higher BMI, more likely to be male and non-Hispanic White, and had higher prevalence of HBP and diabetes.

The ZJU index was positively correlated with the prevalence of kidney stones

The study population was divided into quartiles based on the ZJU index, namely Q1, Q2, Q3 and Q4. Their definitions were as follows: Q1, ≤34.51; Q2, 34.51-39.65; Q3, 39.65-45.57; and Q4: ≥45.57. As shown in **Figure 2**, the prevalence of kidney stones increased significantly with higher ZJU index quartiles (4.09% vs. 7.31% vs. 10.50% vs. 16.90%, $P<0.001$). In the three weighted multivariate logistic regression models, the unadjusted crude model showed a kidney stone risk of 1.057 (95% CI: 1.051-1.062). When covariates were adjusted in Model 1 and Model 2, the OR were 1.059 (95% CI: 1.053-1.066) and 1.210 (95% CI: 1.186-1.234), respectively.

In both the crude model and the adjusted models, when compared to the Q1, participants in Q2, Q3 and Q4 exhibited significantly higher risks of kidney stones (**Table 2**). Notably, in the fully adjusted Model 2, compared to Q1, the risks of kidney stones were 1.758-, 2.728-, and 4.689-fold higher in Q2, Q3 and Q4, respectively. Additionally, trend test showed a statistically significant upward trend of kidney stone risk with the increase of the ZJU index ($P<0.05$).

These results indicate that there exists a strong and consistent association between elevated ZJU index and kidney stone risk.

Non-linearity and threshold effect analysis between the ZJU index and kidney stone risks

As shown in **Figure 3**, restricted cubic spline (RCS) analysis showed a significant non-linear relationship between the ZJU index and kidney stone risk ($P<0.05$; for overall association, $P<0.01$), and identified a turning point at the ZJU index of 38.1. As presented in **Table 3**, when the ZJU index was below 38.1, each standard deviation increase in the ZJU index was significantly associated with a higher risk of kidney stones, with an OR of 1.151 (95% CI: 1.138-1.164; $P<0.05$). Conversely, when the ZJU index exceeded 38.1, the association remained positive but was attenuated, with an OR of 1.098 (95% CI: 1.068-1.129; $P<0.05$).

Furthermore, the likelihood ratio test comparing the traditional logistic regression model and the segmented logistic regression model based on the turning point showed that the latter can more accurately depict the nonlinear relationship between the ZJU index and kidney stone risk.

Subgroup analysis

To evaluate the contribution of the covariates involved in the association observed between the ZJU index and kidney stone risk, we performed subgroup analysis. As shown in **Figure 4**, significant interactions were observed in subgroups of gender, race, BMI, HBP, and diabetes. Specifically, compared with females (OR: 1.045, 95% CI: 1.038-1.053), males showed a stronger association and a higher risk (OR: 1.066, 95% CI: 1.058-1.074). Among racial groups, “Other Race - Including Multi-Racial” exhibited the highest risk (OR: 1.076, 95% CI: 1.058-1.095). Across increasing BMI categories, although the ZJU index remained significantly associated with kidney stone risks, the OR value gradually decreased. Similarly, diabetes and HBP groups also showed significant associations, but the OR values were lower when compared with non-diseased groups.

Table 2. Logistic regression analysis between ZJU with kidney stones

Characteristic	Crude model		Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
ZJU (Per SD increment)	1.057 (1.051-1.062)	<0.001	1.059 (1.053-1.066)	<0.001	1.210 (1.186-1.234)	<0.001
ZJU index (Quartile)						
Q1	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
Q2	1.987 (1.618-2.440)	<0.001	1.766 (1.431-2.179)	<0.001	1.758 (1.423-2.175)	<0.001
Q3	3.099 (2.503-3.838)	<0.001	2.803 (2.236-3.515)	<0.001	2.728 (2.160-3.444)	<0.001
Q4	5.158 (4.269-6.234)	<0.001	5.006 (4.060-6.172)	<0.001	4.689 (3.758-5.851)	<0.001
Per 1-category increase	1.700 (1.608-1.798)	<0.001	1.685 (1.606-1.768)	<0.001	1.658 (1.561-1.762)	<0.001

OR, odds ratio; CI, confidence interval; SD, standard deviation; Q, quartile. Crude model: no covariates were adjusted. Model 1: sex, age, race, educational level, and marital status were adjusted. Model 2: model 1 + Cotinine, Alcohol drink, Diabetes and Hypertension (HBP) were fully adjusted.

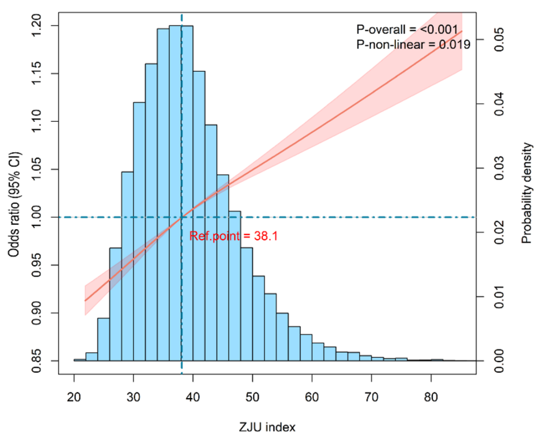

Figure 3. Restricted cubic spline analysis of the association between the Zhejiang University (ZJU) index and kidney stone history. CI, confidence interval.

Table 3. Threshold effect analysis of ZJU on kidney stones using the two-piecewise regression model

ZJU index	OR	95% CI	P
Inflection point			
<38.1	1.151	1.138-1.164	<0.001
≥38.1	1.098	1.068-1.129	<0.001
Likelihood ratio test	χ^2 = 87.84272		<0.001

OR, odds ratio; CI, confidence interval.

These results are consistent with findings reported by Xie et al. [25] in gallstone research, indicating that the ZJU index may be influenced by a variety of factors.

ROC curve for the discriminative ability of the ZJU index

To evaluate the discriminative ability of the ZJU index and its individual components, we plotted the ROC curves. As shown in **Figure 5**, the AUCs (95% CIs), ranked from highest to lowest, were 0.819 (0.810-0.828) for the ZJU index, 0.762 (0.751-0.772) for the ALT/AST ratio, 0.731 (0.720-0.742) for FBG, 0.675 (0.664-0.686) for TG, and 0.611 (0.599-0.623) for BMI. The ZJU index showed significantly greater discriminative ability than the individual components according to paired DeLong tests (all P<0.001), with a sensitivity of 76.2%, a specificity of 71.5%, and an optimal cut-off value of 36.78.

Sensitivity analyses

To evaluate the robustness and reliability of our findings, we conducted PSM and weighted generalized logistic regression analyses as sensitivity analyses. The sample size in the kidney stone group and its matched control group was 2,484 and 4,968 after PSM. The baseline characteristics of the matched samples were presented in Table S1.

Covariates, including age, education, race, marital status, HBP, diabetes, and cotinine levels, were successfully matched (*P*>0.05). Consistent with the previous results, the ZJU index in the kidney stone group was still significantly higher than that in the non-kidney stone group after matching. Subsequent results obtained from the weighted generalized logistic regression analysis (**Table 4**) were highly consistent with the findings derived from the full dataset (**Table 2**). In the fully adjusted Model 2, compared with Q1, participants in Q2, Q3, and Q4 exhibited higher OR (1.577, 2.528, and 3.639, respectively).

These results confirmed that the ZJU index is a robust and reliable indicator associated with

Variable	Group	OR (95% CI)	pvalue	Interaction_pvalue
Age	<=65	1.057 (1.050 to 1.064)	<0.001	0.114
	>65	1.067 (1.056 to 1.077)	<0.001	
Gender	Female	1.045 (1.038 to 1.053)	<0.001	<0.001
	Male	1.066 (1.058 to 1.074)	<0.001	
Race	Mexican American	1.051 (1.036 to 1.067)	<0.001	0.012
	Non−Hispanic Black	1.039 (1.026 to 1.053)	<0.001	
	Non−Hispanic White	1.063 (1.055 to 1.072)	<0.001	
	Other Hispanic	1.069 (1.048 to 1.091)	<0.001	
	Other Race − Including Multi−Racial	1.076 (1.058 to 1.095)	<0.001	
Education	Less Than 9th Grade	1.065 (1.045 to 1.087)	<0.001	0.217
	9−11th Grade	1.062 (1.047 to 1.078)	<0.001	
	High School Grad	1.048 (1.036 to 1.061)	<0.001	
	Some College or AA degree	1.052 (1.043 to 1.062)	<0.001	
	College Graduate or above	1.068 (1.054 to 1.082)	<0.001	
MaritalStatus	Divorced	1.063 (1.049 to 1.077)	<0.001	0.154
	Living with partner	1.050 (1.028 to 1.072)	<0.001	
	Married	1.062 (1.054 to 1.071)	<0.001	
	Never married	1.046 (1.030 to 1.062)	<0.001	
	Separated	1.041 (1.017 to 1.064)	<0.001	
	Widowed	1.043 (1.022 to 1.063)	<0.001	
BMI	Underweight	1.432 (1.127 to 1.820)	0.005	<0.001
	Normal weight	1.185 (1.152 to 1.218)	<0.001	
	Overweight	1.161 (1.137 to 1.185)	<0.001	
	Obesity	1.149 (1.118 to 1.180)	<0.001	
	Severe obesity	1.056 (1.040 to 1.073)	<0.001	
HBP	No	1.061 (1.053 to 1.070)	<0.001	<0.001
	Yes	1.042 (1.034 to 1.050)	<0.001	
diabetes	No	1.057 (1.051 to 1.063)	<0.001	0.031
	Borderline	1.054 (1.021 to 1.088)	0.002	
	Yes	1.038 (1.025 to 1.051)	<0.001	
Cotinine	Q1	1.062 (1.051 to 1.074)	<0.001	0.690
	Q2	1.053 (1.040 to 1.066)	<0.001	
	Q3	1.058 (1.047 to 1.069)	<0.001	
	Q4	1.054 (1.043 to 1.066)	<0.001	
ALCOHOL	NEVER	1.060 (1.048 to 1.073)	<0.001	0.728
	FORMER	1.045 (1.027 to 1.065)	<0.001	
	MILD	1.059 (1.050 to 1.068)	<0.001	
	MODERATE	1.053 (1.039 to 1.066)	<0.001	
	HEAVY	1.058 (1.046 to 1.070)	<0.001	

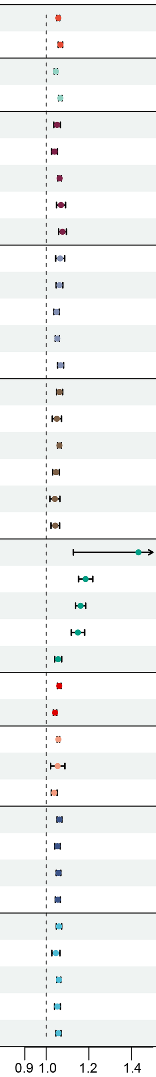

Figure 4. Association between ZJU and the risk of kidney stones in various subgroups. OR, odds ratio; CI, confidence interval; BMI, body mass index; HBP, high blood pressure; AA, associate degree.

kidney stone risk, with minimal influence from potential confounding covariates.

Discussion

Kidney stone disease is a condition caused by the combined effects of multiple factors, with its incidence continuing to rise globally, imposing a heavy physical, mental and financial burden on patients, as well as a serious challenge to the public healthcare system. Therefore, exploring effective and reliable tools for distinguishing the risk of kidney stones is of great significance for the development of prevention and treatment strategies. This study represents the first exploration of the association between the ZJU index (a comprehensive indicator integrated from multiple factors related to kidney stones) and kidney stone risk, and demonstrated that the ZJU index is a valuable tool for risk stratification and screening in kidney stone management.

In the study population included, the ZJU index was significant higher in the kidney stone group than that in the non-stone control group. Both weighted generalized linear models and quartile regression analyses revealed a significant positive correlation between elevated ZJU index levels and the prevalence of kidney stones.

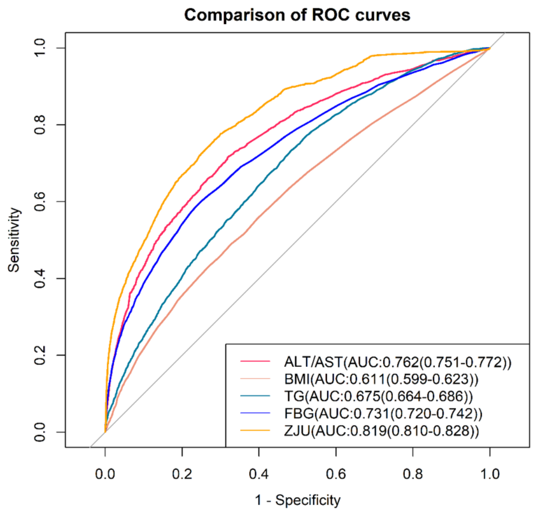

Figure 5. Receiver operating characteristic (ROC) curve analysis comparing the discriminative ability of the Zhejiang University (ZJU) index, body mass index (BMI), triglycerides (TG), fasting blood glucose (FBG), and alanine aminotransferase-to-aspartate aminotransferase ratio (ALT/AST ratio) for identifying participants with a history of kidney stones. AUC, area under the curve; CI, confidence interval.

This relationship demonstrated a nonlinear trend in RCS analysis, identifying a critical turning point at 38.1, suggesting that this value may serve as a potential threshold for distinguishing kidney stone risk. Subsequent subgroup analyses and sensitivity analyses post PSM further confirmed that the association between the ZJU index and kidney stone risk was minimally influenced by confounding factors, thereby demonstrating its stability and reliability. The ROC curve analysis showed that the ZJU index has significantly superior discriminative ability compared to other individual indicators assessed, with a sensitivity of 76.2%, a specificity of 71.5%, and an optimal cutoff value of 36.78, indicating that the discriminative ability of the ZJU index may not lie in any single component, but in its ability to summarize multiple metabolic abnormalities that commonly coexist in individuals at risk of kidney stones.

Although there are currently no published studies specifically exploring the relationship between the ZJU Index and kidney stones, a large number of metabolic studies have highlighted that various components of the ZJU Index are closely related to the occurrence and development of kidney stones: 1) Increased BMI, increased waist circumference, reduced HDL-C, and elevated FBG have been demonstrated to be independent risk factors for kidney stones [26-28]; 2) Insulin resistance, elevated TG levels, and low HDL-C levels are recognized as significant contributors to kidney stone formation [17, 29]; 3) Abnormal lipid profiles may increase the risk of kidney stones through mechanisms such as impaired insulin sensitivity, chronic inflammation, and heightened oxidative stress [16, 17]; 4) Evidence suggests that ALT and AST may also increase the risk of kidney stones [13, 14, 30, 31]. By integrating these diverse factors, the ZJU index offers a comprehensive perspective on metabolic health, providing a more robust assessment of kidney stone risk compared to individual components [4, 5]. The ZJU index should be interpreted as an indicator of metabolic burden rather than a disease specific marker for kidney stone. Its association with kidney stones may reflect the cumulative contribution of metabolic abnormalities such as adiposity, dyslipidemia, impaired glucose metabolism.

In the subgroup analysis performed to evaluate the stability of the association between the ZJU index and kidney stones, significant interactions were observed in terms of gender, race, BMI, HBP, and diabetes. We observed that the incidence of kidney stones was significantly higher in males than females, and individuals identified as "Other Race - Including Multi-Racial" demonstrated the highest risk. Among patients with increasing severity of obesity, HBP, and diabetes, the association between ZJU index and kidney stone risk gradually weakened [32, 33], which is consistent with the findings reported by Xie et al. [25] in their study focused on the ZJU index and the gallstones. Therefore, although the ZJU index exhibits a significant association with kidney stone risk across all subgroups, the OR values may be influenced by multiple factors. As BMI increases or as HBP and diabetes are diagnosed, the degree of metabolic abnormality may worsen; however, factors such as treatment, disease management, and other confounding variables may contribute to a reduction in kidney stone risk. Consequently, when evaluating the relationship between the ZJU index and kidney stone risk, it is essential to consider the interplay of these various factors comprehensively.

Although this study revealed a significant association between the ZJU Index and the risk of

Table 4. Logistic regression analysis between ZJU with kidney stones for PSM-matched samples

Characteristic	Crude Model		Model 1		Model 2	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
ZJU (Per SD increment)	1.048 (1.041-1.055)	<0.001	1.050 (1.042-1.057)	<0.001	1.289 (1.242-1.338)	<0.001
ZJU index (Quartile)						
Q1	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
Q2	1.457 (1.223-1.737)	<0.001	1.519 (1.268-1.820)	<0.001	1.577 (1.312-1.895)	<0.001
Q3	2.203 (1.832-2.649)	<0.001	2.327 (1.908-2.839)	<0.001	2.528 (2.034-3.142)	<0.001
Q4	2.975 (2.522-3.510)	<0.001	3.142 (2.636-3.746)	<0.001	3.639 (2.985-4.438)	<0.001
Per 1-category increase	1.438 (1.342-1.553)	<0.001	1.465 (1.370-1.582)	<0.001	1.538 (1.263-1.883)	<0.001

PSM, propensity score matching; OR, odds ratio; CI, confidence interval; SD, standard deviation; Q, quartile.

kidney stones, the underlying mechanism is still unclear. Recently, a number of researches indicate that the ZJU index is closely linked to lipid regulation, insulin resistance, obesity, and the risk of diseases such as NAFLD and OS [11, 12]. Furthermore, there is a significant association between kidney stones and NAFLD, and these two conditions share overlapping metabolic pathways [13, 14]. Therefore, the association between the ZJU index and kidney stone risk may be mediated through multiple metabolic mechanisms. It is speculated that elevated ZJU index levels may be closely associated with dysregulated lipid metabolism, abnormal urinary composition, and reduced insulin sensitivity, and these metabolic alterations potentially contribute to the formation of urinary crystals, ultimately promoting kidney stone development.

However, this study has certain limitations. First, the cross-sectional design of the study precludes the establishment of causal relationships. Second, critical factors such as dietary habits and physical activity, which may influence the risk of kidney stones, were not fully accounted for, potentially impacting the study's conclusions. Future research should focus on multicenter, prospective studies to validate the applicability of the ZJU index and explore its underlying molecular mechanisms in kidney stone formation. These efforts would provide more robust evidence to guide clinical practice and optimize preventive strategies.

Taken together, this study found that the ZJU index was significantly positively correlated with the risk of kidney stones, and it exhibited superior discriminative ability compared to its components. Due to its wide accessibility and cost-effectiveness based on individual general characteristics and routine blood biochemical indicators, the ZJU index is expected to become a valuable screening tool for large-scale high-risk populations.

Conclusions

Higher ZJU index was strongly associated with kidney stone history in a nationally representative US sample. As a routine-data composite metabolic measure, the ZJU index may help inform population risk stratification and prevention-oriented public health planning. However, longitudinal studies are warranted to confirm temporality and assess real-world applicability.

Disclosure of conflict of interest

None

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Table S1. Baseline data of PSM participants

Characteristics	Overall	Non-stone controls	Kidney stone patients	P
n	7452	4968	2484	
Age, (years)	56.42±16.54	56.58±16.76	56.10±16.10	0.239
Gender, n (%)				0.811
Female	3254 (43.7)	2164 (43.6)	1090 (43.9)	
Male	4198 (56.3)	2804 (56.4)	1394 (56.1)	
Race, n (%)				0.979
Mexican American	978 (13.1)	653 (13.1)	325 (13.1)	
Non-Hispanic Black	935 (12.5)	625 (12.6)	310 (12.5)	
Non-Hispanic White	4138 (55.5)	2766 (55.7)	1372 (55.2)	
Other Hispanic	785 (10.5)	516 (10.4)	269 (10.8)	
Other Race - Including Multi-Racial	616 (8.3)	408 (8.2)	208 (8.4)	
Education, n (%)				0.003
Less Than 9th Grade	757 (10.2)	494 (9.9)	263 (10.6)	
9-11th Grade	1069 (14.3)	713 (14.4)	356 (14.3)	
High School Grad	1686 (22.6)	1125 (22.6)	561 (22.6)	
Some College or AA degree	2377 (31.9)	1574 (31.7)	803 (32.3)	
College Graduate or above	1563 (21.0)	1062 (21.4)	501 (20.2)	
Marital Status, n (%)				0.626
Divorced/Widowed	1069 (23.4)	1156 (23.3)	583 (23.5)	
Married/Living with partner	4794 (64.4)	3213 (54.7)	1581 (63.6)	
Never married/Separated	919 (12.3)	599 (12.0)	320 (12.9)	
BMI, (kg/m^2)	29.96 (6.89)	29.67 (6.80)	30.54 (7.04)	
HBP, n (%)				0.838
No	3667 (49.2)	2440 (49.1)	1227 (49.4)	
Yes	3785 (50.8)	2528 (50.9)	1257 (50.6)	
Diabetes, n (%)				0.246
No	5608 (75.3)	3767 (75.8)	1841 (74.1)	
Borderline	221 (3.0)	141 (2.8)	80 (3.2)	
Yes	1623 (21.8)	1060 (21.3)	563 (22.7)	
Cotinine, (ng/mL)	62.72±40.18	60.75±37.50	66.66±45.32	0.086
Alcohol, n (%)				0.312
NEVER	1419 (19.0)	955 (19.2)	464 (18.7)	
FORMER	401 (5.4)	257 (5.2)	144 (5.8)	
MILD	3020 (40.5)	1988 (40.0)	1032 (41.5)	
MODERATE	1217 (16.3)	811 (16.3)	406 (16.3)	
HEAVY	1395 (18.7)	957 (19.3)	438 (17.6)	
ZJU_INDEX	42.48±8.73	41.30±8.39	44.83±8.94	<0.001