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Association Between Cardio-Kidney-Metabolic Syndrome and Overactive Bladder: Mediation by Systemic Inflammation, Depression, and Shared Metabolic Signatures

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Posted Date: 16 March 2026

doi: 10.20944/preprints202603.1096.v1

Keywords:

overactive bladder; cardio-kidney-metabolic syndrome; systemic inflammation; depression; metabolomics

 doi:10.20944/preprints202603.1096.v1

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Association Between Cardio-Kidney-Metabolic Syndrome and Overactive Bladder: Mediation by Systemic Inflammation, Depression, and Shared Metabolic Signatures

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Abstract

Introduction Overactive bladder (OAB) frequently co-occurs with cardiovascular-kidney-metabolic (CKM) syndrome; however, the complex interplay of systemic inflammation, psychological distress, and metabolic dysregulation driving this connection remains poorly defined. This study aimed to elucidate these multidimensional associations and identify shared metabolic patterns between OAB and CKM-related conditions. **Methods** We analyzed data from 11,836 participants in the National Health and Nutrition Examination Survey (2005–2018). CKM stages were classified using American Heart Association criteria, while OAB severity, systemic inflammation, and depression were assessed via the Overactive Bladder Symptom Score, neutrophil-to-high-density lipoprotein cholesterol ratio (NHR), and Patient Health Questionnaire-9, respectively. We utilized survey-weighted multivariable regression and mediation analysis. Furthermore, two-sample Mendelian randomization (MR) analyses using genome-wide association study datasets were conducted to identify causal metabolites. **Results** Higher CKM stages were significantly associated with increased OAB severity. Elevated NHR and depression scores were independently linked to OAB. Notably, a significant synergistic interaction was observed: moderate inflammation amplified the impact of depressive symptoms on OAB. Mediation analyses demonstrated that NHR, depression, and their interaction significantly mediated the relationship between CKM stage and OAB. MR analysis identified specific causal lipid, amino acid, and energy-related metabolites for OAB, exhibiting substantial overlap with CKM metabolic signatures. **Discussion & Conclusion** CKM progression, systemic inflammation, and depression are robustly associated with OAB, linked through neuro-inflammatory and psychological pathways. OAB appears to be a manifestation of systemic dysregulation shared with CKM syndrome, necessitating integrated management strategies addressing cardiometabolic health and psychological well-being.

Keywords: overactive bladder; cardio-kidney-metabolic syndrome; systemic inflammation; depression; metabolomics

 doi:10.20944/preprints202603.1096.v1

1. Introduction

Overactive bladder (OAB) is a clinical syndrome primarily characterized by urgency, often accompanied by increased urinary frequency and nocturia. Some patients may also experience urge urinary incontinence (UUI).[1] This condition has a high prevalence worldwide, particularly among the elderly. Data indicates that the overall prevalence of OAB in the United States was 16.5% during 2000-2001, and by 2021-2022, this rate had significantly risen to 38.5%.[2] As a chronic condition, OAB significantly impacts patients' quality of life, not only disrupting their social and work functions but also leading to feelings of embarrassment, shame, and psychological burden.[3]

Cardio-kidney-metabolic syndrome (CKM), introduced by the American Heart Association (AHA), refers to the highly coupled pathological processes between metabolic risk factors, chronic kidney disease (CKD), and cardiovascular diseases, ultimately leading to multi-organ dysfunction. This construct reflects the interplay between metabolic dysregulation, chronic low-grade inflammation, and altered neurohumoral control.[4] While CKM has been linked to cardiovascular and renal outcomes, its relevance to lower urinary tract disorders, including OAB, remains poorly defined.

Depression is a common mental disorder, characterized by persistent low mood, reduced interest, and lack of energy.[5] Persistent depression can significantly coampromise an individual's social functioning and physical health.[6] The patient health questionnaire-9 (PHQ-9) is a widely used tool for measuring depression in epidemiological surveys and clinical screenings, with good reliability and validity.[7–9] Previous studies have shown that as the severity of OAB increases, patients' mental health deteriorates significantly, and the risk of developing depression rises. Depression itself has also been established as an independent risk factor for OAB.[10–12] This suggests that the development of OAB is not only associated with urinary system dysfunction but may also be influenced by psychological and neurological factors.

In recent years, growing attention has been directed to the role of inflammatory factors in the pathogenesis of depression. The neutrophil to high-density lipoprotein cholesterol ratio (NHR) is a novel indicator reflecting systemic inflammation, which has been shown to have a positive correlation with the risk of depression,[13,14] suggesting that it may serve as a potential inflammatory biomarker for depression.

Despite established links between CKM and psychiatric disorders,[15] the association between CKM and OAB represents a critical knowledge gap. Current research lacks the depth to explain the neuro-inflammatory and psychological interplay that may drive this connection. Additionally, the shared metabolic foundation between OAB and systemic CKM-related conditions remains undefined.

Therefore, leveraging nationwide cohort data from the National Health and Nutrition Examination Survey (NHANES) and large-scale genome-wide association study (GWAS) datasets, this study aims to systematically assess the impact of CKM staging on OAB risk and further investigate the potential mechanisms of inflammatory status and psychological statusin this relationship, and to further explore metabolic patterns associated with OAB and their convergence with CKM related symptoms. By identifying multidimensional risk profiles, we seek to establish mechanistic and evidence-based foundations for personalized OAB prevention and management.

2. Materials and Methods

2.1. Study Design and Population

The NHANES is a nationally representative program that monitors the health and nutritional parameters in the U.S. population. Conducted by the National Center for Health Statistics (NCHS), it implements standardized data collection protocols encompassing household interviews, clinical examinations, and biospecimen analyses. The participant consent process was carried out according to NHANES protocols, ensuring participants were fully informed about the nature of the study and their rights prior to participation. Specifically, ethical approval was granted by the NCHS Ethics

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Review Board, under protocols including Protocol #2005-06, Continuation of Protocol #2005-06, Protocol #2011-17, and Continuation of Protocol #2011-17 (available at http://medbox.iiab.me/modules/en-cdc/www.cdc.gov/nchs/nhanes/irba98.htm). No personally identifiable information was used in the present study. Detailed methodological specifications regarding sampling framework, interview protocols, and laboratory procedures are documented in manuals.[16] All procedures involving human participants were conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical guidelines. Our report followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[17]

Analytical data were derived from 7 continuous NHANES cycles from 2005-2006 to 2017-2018 (available at www.cdc.gov/nchs/nhanes). Participants aged 18 and above were included, and were excluded if they had missing data on CKM stage (n = 53,612), PHQ-9 score (n = 1,345), OAB score (n = 48), NHR (n = 166), demographics feature (n = 1,255) or other covariates (n = 1,928), and the final analytical cohort comprised 11,836 participants (Figure 1).

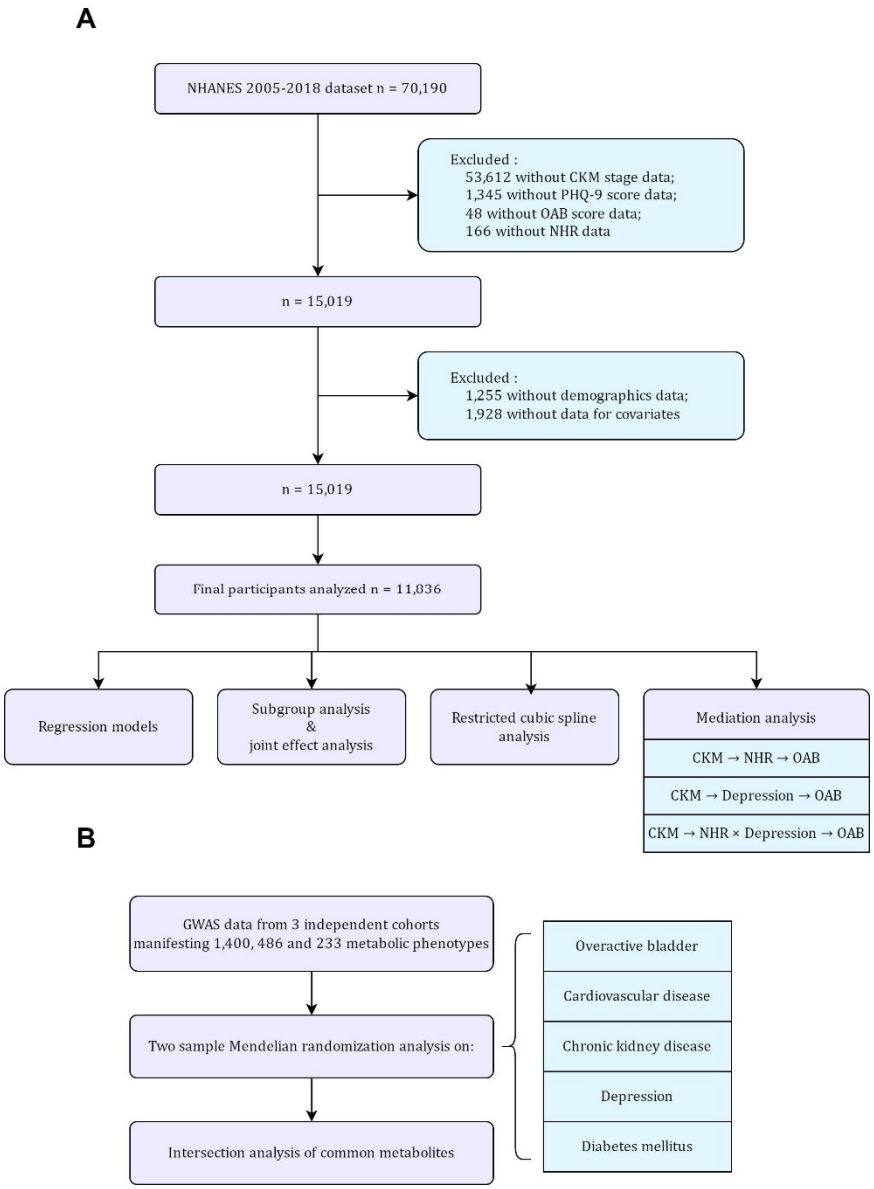

Figure 1. Flow chart of study design. (A) NHANES cohort exploration of the association and mechanism between OAB and CKM. (B) Investigation of common upstream metabolites within the Mendelian

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randomization analysis framework. CKM, cardiovascular-kidney-metabolic syndrome. PHQ-9, patient health questionnaire-9. OAB, overactive bladder. NHR, neutrophil to high-density lipoprotein cholesterol ratio.

2.2. Definition and Measurement

2.2.1. CKM Stage

CKM stages were categorized according to the 2023 AHA Presidential Advisory on CKM Health,[18] utilizing a five-tier classification system (stages 0 to 4):

Stage 0 included individuals with no metabolic abnormalities, defined by normal BMI (<23 kg/m^2 for Asian populations; <25 kg/m^2 for other ethnic groups), waist circumference below thresholds (Asian women/men: <80/<90 cm; others: <88/<102 cm), normoglycemia, normotension, normal lipid profiles, and absence of diabetes, CKD, or clinical/subclinical cardiovascular disease (CVD).

Stage 1 is characterized by elevated BMI (≥23 kg/m^2 for Asians; ≥25 kg/m^2 for others), elevated waist circumference (Asian women/men: ≥80/≥90 cm; others: ≥88/≥102 cm), or prediabetes (HbA1c 5.7–6.4% or fasting glucose 100–125 mg/dL), without other metabolic risk factors or CKD.

Stage 2 refers to the presence of one or more metabolic risk factors (hypertriglyceridemia, hypertension, diabetes, metabolic syndrome) or moderate- to high-risk CKD per Kidney Disease Improving Global Outcomes (KDIGO) criteria,[18] based on estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio.

Stage 3 included two high-risk subgroups: (1) very high-risk CKD (KDIGO criteria, e.g., eGFR <30 mL/min/1.73m^2) or (2) ≥20% 10-year CVD risk. The 10-year CVD risk was estimated with the AHA Predicting Risk of CVD EVENTs (PREVENT) equations.[19] This algorithm incorporates age (30-79 years), total cholesterol (130-320 mg/dL), HDL-C (20-100 mg/dL), systolic blood pressure (90-200 mmHg), BMI (18.5-<40 kg/m^2), and eGFR (15-150 mL/min/1.73m^2). Values exceeding these ranges were truncated to boundary limits (e.g., age >79 set to 79) to avoid underestimation.

Stage 4 included individuals with established clinical CVD, including coronary heart disease, angina, heart attack, heart failure, or stroke. Advanced CKM stages (stages 3-4) denote high CVD risk or confirmed CVD, whereas nonadvanced stages (0-2) reflect lower-risk profiles.

2.2.2. NHR, Inflammation Indicator

NHR, leveraged as the indicator of inflammation in this study, is derived by dividing neutrophil counts (10^3 cells/μL) by HDL-C levels (mmol/L). Neutrophil counts were measured using Beckman Coulter DxH 800 instrument. HDL-C concentrations within venous blood samples obtained after 8-hour fasting were quantified using Roche Modular P and Roche Cobas 6000 chemistry analyzers.

2.2.3. PHQ-9 Score and Depression Grade

PHQ-9 was employed during in-person MEC interviews to evaluate depression-related symptoms within the preceding two weeks. Participants quantified their symptom frequency through a scale of 0-3, encompassing nine indicators: (1) diminished interest, (2) low mood, (3) sleep disturbance, (4) fatigue, (5) appetite changes, (6) low self-esteem, (7) concentration problems, (8) observable psychomotor alterations, and (9) suicidal ideation. Scoring interpretation follows a cumulative metric, with established clinical thresholds stratifying depression grade: minimal (1-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27).[20]

2.2.4. OAB Score

OAB was defined as a pathological hypersensitivity disorder of the urinary system, manifested by UUI and nocturia. Diagnostic data for OAB diagnosis was obtained through standardized questionnaires administered by trained investigators during structured in-person interviews. UUI was determined with the question: "*During the past 12 months, have you leaked or lost control of even a small amount of urine with an urge or pressure to urinate, and you could not get to the toilet fast enough?*", with symptom frequency quantified by the query: "*How frequently does this occur?*". Concurrently,

 doi:10.20944/preprints202603.1096.v1

nocturia was assessed via the question: "*During the past 30 days, how many times per night did you most typically get up to urinate, from the time you went to bed at night until the time you got up in the morning?*". The OAB score was qualified using the Overactive Bladder Symptom Score (OABSS), as outlined in Table S1.[11] Participants scoring ≥3 on the OABSS were categorized as OAB-positive,[21,22] and this study utilized the total OAB score as the outcome measure to assess OAB severity.

2.2.5. Covariates

To minimize potential confounding effects, several covariates were incorporated into the adjusted models based on established studies considering CKM symptom, NHR, PHQ-9 or OAB.[12,23,24] The adjusted Model 2 integrated sociodemographic parameters comprising age, gender, race, education level, marital status, and poverty status (classified as below or above the poverty threshold based on family poverty-to-income ratio (PIR)), coupled with eGFR assessments. Model 3 further incorporated behavioral and clinical factors including smoking status, alcohol consumption, hypertension, cardiovascular diseases, diabetes, and stroke. Detailed documentation of variable acquisition protocols and assessment methodologies is publicly available through the NHANES repository (accessible at www.cdc.gov/nchs/nhanes).

2.2.6. GWAS Data for Metabolomic Features

Serum metabolomic data were obtained from published GWAS metabolomic datasets, including panels of 1400, 486, and 233 metabolite phenotypes, respectively.[25–27] These panels covered multiple biochemical classes, including lipids and lipoprotein-related traits, fatty acids, amino acid–related metabolites, bile acids, organic acids, and other small molecules.

2.2.7. GWAS Data for Disease Outcomes

For OAB, genetic association data was obtained from the UK Biobank for the phenotype "Bladder: Calcified/Contracted/Overactive" (GWAS ID: ukb-b-373) from the IEU OpenGWAS project database, reported by Zhang et al.[28] The analysis included 463,010 participants and 9,851,867 SNPs. GWAS summary statistics for CVD, CKD, DM and depression were sourced from the FinnGen consortium release R11 corresponding to the phenotypes FG_CVD(Cardiovascular diseases (excluding rheumatic etc)), N14_CHRONKIDNEYDIS (Chronic kidney disease), T2D (Type 2 diabetes, definitions combined), and F5_DEPRESSIO (Depression), respectively. All outcomes were ascertained through nationwide Finnish health registries and integrated using standardized diagnostic codes. Detailed information regarding the FinnGen study design, phenotype definitions, genotyping procedures, and quality control has been reported previously and is available at https://r11.risteys.finngen.fi/.[29]

2.3. Data Analysis

In alignment with the Centers for Disease Control and Prevention (CDC) guidelines, we implemented appropriate sampling weights in data assessment.[30] Participant characteristics underwent stratification based on CKM stages. Subsequently, continuous variables were reported with the mean ± standard deviation (SD), and categorical variables were described with percentages. Group differences were assessed using survey-weighted Kruskal–Wallis tests for continuous variables and survey-weighted chi-square tests for categorical variables. To elucidate pairwise relationships between each exposure (CKM stage, NHR, and PHQ-9 score) and OAB score, we constructed a hierarchical linear regression architecture comprising: Model 1, a crude model without any modifications; Model 2, adjusted for age, race, education level, marital status, poverty status and eGFR; and Model 3, further adjusted for smoking status, alcohol consumption, hypertension, cardiovascular diseases, diabetes, and stroke. We quantified the strength of associations using regression β coefficients with 95% confidence intervals (CI). Further, potential effect modification between NHR and PHQ-9 score was evaluated through subgroup and joint effect analyses. Then,

 doi:10.20944/preprints202603.1096.v1

restricted cubic spline (RCS) analyses were applied to assess potential nonlinear associations between each exposure and OAB score.

Mediation analyses were performed to illustrate how NHR and PHQ-9 score intervene the association of CKM stage with OAB score. The total, direct, and indirect effects were estimated using survey-weighted regression models, with indirect effects calculated using the product-of-coefficients method. The proportion mediated was defined as the ratio of the indirect effect to the total effect. Statistical uncertainty was assessed using 2000 bootstrap resamples applying the survey design. 95% CIs were calculated based on the distributions generated by bootstrap, and the null effect hypothesis was tested by a two-tailed p-value.

Subsequently, two sample Mendelian randomization analyses were adopted for metabolites' effect on OAB within three independent metabolite datasets, where the inverse-variance weighted method was the primary method to generate causal estimates, and various sensitivity analyses including heterogeneity test, pleiotropy test, leave-one-out and MR-PRESSO test were conducted to ensure robustness. Similar causal analyses were conducted for CKM related outcomes, including CKD, CVD, diabetes, and depression. Shared metabolic patterns were evaluated by comparing sets of significant metabolites across outcomes, and overlap was summarized using set based approaches and visualized with UpSet plots.

All statistical analyses were executed with R 4.5.0 software (http://www.R-project.org; The R Foundation), with significance α-level set at 0.05.

3. Results

3.1. Baseline Characteristics

From 2005 to 2018, a total of 11,836 participants with an average age of 47.98 ±16.84 were enrolled in analysis (Figure 1). As illustrated in Table 1, participants' OAB score and occurrence of OAB differed among CKM stage groups (P < 0.001). As the CKM classification varied from 0 to 4, a fluctuating upward trend was observed in both OAB score and the incidence of OAB. Statistically significant differences were observed in age (P < 0.001), gender (P < 0.001), race (P < 0.001), education (P < 0.001), marital status (P < 0.001), poverty status (P = 0.008), smoking habits (P < 0.001) and alcohol consumption (P < 0.001) across the CKM stages.

Table 1. Participant characteristics based on CKM stages: NHANES 2005-2018, weighted.

Characteristic	**CKM Stage**						***P*-value** [b]
	Overall N = 11,836[a]	**0** N = 983[a]	**1** N = 2,209[a]	**2** N = 4,885[a]	**3** N = 2,526[a]	**4** N = 1,233[a]	
Age	47.98±(16.84)	35.98±(13.38)	41.46±(14.40)	54.15±(15.28)	42.26±(15.00)	65.14±(12.37)	<0.001
Gender							<0.001
Male	5,686(48.22%)	298(31.02%)	763(36.81%)	1,732(34.30%)	2,189(88.16%)	704(52.48%)	
Female	6,150(51.78%)	685(68.98%)	1,446(63.19%)	3,153(65.70%)	337(11.84%)	529(47.52%)	
Race							<0.001
Mexican American	1,766(7.994%)	110(5.296%)	391(9.530%)	710(6.885%)	464(10.95%)	91(4.430%)	
Non-Hispanic White	5,542(69.68%)	490(72.34%)	943(67.03%)	2,230(70.77%)	1,165(66.92%)	714(75.55%)	
Non-Hispanic Black	2,352(9.999%)	131(7.753%)	470(11.84%)	1,090(10.71%)	378(7.302%)	283(12.07%)	
Other	2,176(12.33%)	252(14.61%)	405(11.60%)	855(11.64%)	519(14.83%)	145(7.949%)	
Education							<0.001

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Below high school	2,608(14.61%)	107(8.222%)	415(12.02%)	1,134(14.95%)	592(15.85%)	360(23.59%)	
High School graduate	2,708(23.35%)	180(19.25%)	443(21.00%)	1,146(24.80%)	612(23.58%)	327(26.66%)	
Some college or AA degree	3,607(31.53%)	300(27.83%)	702(31.33%)	1,508(32.76%)	747(31.90%)	350(29.62%)	
College graduate or above	2,913(30.51%)	396(44.69%)	649(35.64%)	1,097(27.49%)	575(28.67%)	196(20.14%)	
Marital status							<0.001
Married	6,328(55.61%)	461(46.55%)	1,128(53.97%)	2,633(58.34%)	1,440(55.45%)	666(58.06%)	
Single	4,545(36.03%)	427(41.32%)	852(36.56%)	1,962(36.07%)	790(33.07%)	514(36.43%)	
Living with a partner	963(8.361%)	95(12.13%)	229(9.468%)	290(5.594%)	296(11.49%)	53(5.505%)	
Poverty status							0.008
Poor	2,284(13.65%)	164(11.80%)	447(13.47%)	911(12.34%)	502(15.58%)	260(17.03%)	
Not poor	9,552(86.35%)	819(88.20%)	1,762(86.53%)	3,974(87.66%)	2,024(84.42%)	973(82.97%)	
eGFR	94.00±(21.74)	104.46±(17.81)	101.73±(18.08)	89.87±(20.03)	97.30±(21.41)	72.82±(23.47)	<0.001
Smoking	2,282(19.78%)	176(20.67%)	372(16.25%)	876(17.90%)	597(24.60%)	261(23.14%)	<0.001
Alcohol	9.03±(20.94)	11.33±(22.19)	8.21±(19.54)	8.52±(20.57)	10.67±(23.02)	6.27±(17.79)	<0.001
Hypertension	4,451(33.98%)	0(0%)	0(0%)	2,586(51.62%)	927(34.36%)	938(75.57%)	<0.001
CVD	927(6.364%)	0(0%)	0(0%)	0(0%)	0(0%)	927(75.78%)	<0.001
Stroke	457(2.986%)	0(0%)	0(0%)	0(0%)	0(0%)	457(35.56%)	<0.001
Diabetes	1,855(11.63%)	25(2.071%)	100(4.196%)	803(12.58%)	462(13.53%)	465(31.60%)	<0.001
NHR	0.08±(0.05)	0.06±(0.03)	0.07±(0.03)	0.08±(0.05)	0.11±(0.05)	0.10±(0.05)	<0.001
PHQ-9 score	2.99±(4.02)	2.52±(3.45)	2.80±(3.80)	3.04±(4.06)	2.87±(3.91)	4.15±(4.98)	<0.001
Depression grade							<0.001
None	9,029(77.22%)	800(81.41%)	1,746(79.38%)	3,687(76.59%)	1,987(78.09%)	809(67.62%)	
Mild	1,845(15.25%)	128(14.08%)	329(14.10%)	791(15.49%)	360(15.17%)	237(18.56%)	
Moderate	610(4.897%)	42(3.159%)	83(3.994%)	261(5.270%)	114(4.395%)	110(8.789%)	
Moderate to severe	248(1.864%)	10(0.861%)	40(2.083%)	108(1.946%)	45(1.707%)	45(2.536%)	
Severe	104(0.767%)	3(0.494%)	11(0.440%)	38(0.707%)	20(0.643%)	32(2.497%)	
OAB score	1.30 (1.23)	0.85 (0.95)	1.08 (1.08)	1.49 (1.24)	1.05 (1.11)	2.14 (1.48)	<0.001
OAB group							<0.001
Non-overactive bladder	9,383(83.57%)	919(94.02%)	1,927(88.96%)	3,657(79.99%)	2,161(88.40%)	719(61.46%)	
Overactive bladder	2,453(16.43%)	64(5.976%)	282(11.04%)	1,228(20.01%)	365(11.60%)	514(38.54%)	

CKM, cardiovascular-kidney-metabolic syndrome. eGFR, estimated glomerular filtration rate. UACR, urinary albumin-to-creatinine ratio. CVD, cardiovascular disease. NHR, neutrophil to high-density lipoprotein

 doi:10.20944/preprints202603.1096.v1

cholesterol ratio. PHQ-9, patient health questionnaire-9. OAB, overactive bladder. a. N (unweighted) (%); Mean±(SD). b. Design-based Kruskal-Wallis test; Pearson's X^2: Rao & Scott adjustment.

3.2. Associations of CKM Stage, Inflammation, and Depression with OAB Score

Table 2 summarizes the associations between CKM stages, NHR, PHQ-9 score, and OAB score across three linear regression models, with CKM stage 0 serving as the reference group. In the fully adjusted model, CKM stages 1, 2, and 3 remained significantly associated with higher OAB scores. Specifically, compared with CKM stage 0, CKM stage 1 was associated with an increased OAB score (β = 0.105, 95% CI [0.012, 0.198], P < 0.05), as was CKM stage 2 (β = 0.131, 95% CI [0.034, 0.228], P < 0.05) and CKM stage 3 (β = 0.175, 95% CI [0.064, 0.286], P < 0.05). A significant positive trend in OAB score was observed with increasing CKM stage across all three models (all P ≤ 0.01). In contrast, the association between CKM stage 4 and OAB score was attenuated and did not reach statistical significance in the fully adjusted model (β = 0.401, 95% CI [-0.057, 0.858], P = 0.089).

Table 2. Association among CKM stage, NHR, PHQ-9 score and OAB score by logistic regression analyses.

Characteristic	Model 1		Model 2		Model 3	
	Beta (95% CI)	***P*-value**	**Beta (95% CI)**	***P*-value**	**Beta (95% CI)**	***P*-value**
CKM stage						
0	Reference		Reference		Reference	
1	0.230 (0.134, 0.326)	<0.001	0.095 (0.002, 0.189)	0.048	0.105 (0.012, 0.198)	0.029
2	0.639 (0.551, 0.728)	<0.001	0.201 (0.111, 0.292)	<0.001	0.131 (0.034, 0.228)	0.010
3	0.200 (0.100, 0.299)	<0.001	0.264 (0.154, 0.374)	<0.001	0.175 (0.064, 0.286)	0.003
4	1.281 (1.150, 1.411)	<0.001	0.635 (0.492, 0.777)	<0.001	*0.401 (-0.057, 0.858)*	*0.089*
P for trend	0.186 (0.157, 0.216)	<0.001	0.127 (0.095, 0.159)	<0.001	0.054 (0.019, 0.088)	0.003
NHR	1.317 (0.655, 1.979)	<0.001	1.992 (1.195, 2.789)	<0.001	1.192 (0.577, 1.806)	<0.001
PHQ-9 score	0.077 (0.068, 0.085)	<0.001	0.067 (0.059, 0.076)	<0.001	0.062 (0.054, 0.071)	<0.001

OR, odds ratio. 95% CI: 95% confidence interval. CKM: cardiovascular-kidney-metabolic syndrome. NHR, neutrophil to high-density lipoprotein cholesterol ratio. PHQ-9, patient health questionnaire-9. OAB, overactive bladder. Total observations analyzed was 11,836. P-values were derived from Wald tests with design-adjusted t-distributions. Model 1: no covariates adjusted. Model 2: adjusted for age, gender, race, education level, marital status, poverty status and eGFR. Model 3: further adjusted for smoking, alcohol consumption, hypertension, cardiovascular diseases, diabetes and stroke.

NHR showed a robust positive association with OAB score in all regression models. In the fully adjusted model, higher NHR was associated with a higher OAB score (β = 1.192, 95% CI [0.577, 1.806], P < 0.001). Similarly, PHQ-9 score was positively correlated with OAB score across all models, with the association remaining significant after full adjustment (β = 0.062, 95% CI [0.054, 0.071], P < 0.001).

To identify the potential interaction between NHR and depression, we performed joint effect analysis and subgroup analysis. As previously mentioned, depression grade was categorized based

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on the PHQ-9 score into minimal (1-4), mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27).[20] In the joint effect analysis, combinations of medium or high NHR layers with mild to severe depression grades were generally associated with higher OAB scores compared with the reference group of low NHR and no depression (Figure 2). The combination of high NHR and severe depression was associated with the greatest increase in OAB score (β = 0.787, 95% CI [0.201, 1.373], P = 0.009). A significant linear interaction between NHR layers and depression grades was observed (β = 0.062, 95% CI [0.053, 0.070], P < 0.001), indicating that the effect of NHR on OAB score varied by depression severity and vice versa. Subgroup analyses stratified by NHR tertiles further supported this interaction (Table 3). Across most NHR strata, increasing depression severity was associated with higher OAB scores, although the association for moderate to severe depression was not statistically significant in the low NHR layer (P = 0.118). Notably, the association between depression and OAB score appeared strongest in the medium NHR layer. Within this group, mild depression was associated with an increase in OAB score (β = 0.470, 95% CI [0.314, 0.624,] P < 0.001), with progressively stronger associations observed for moderate to severe (β = 1.101, 95% CI [0.794, 1.407], P < 0.001) and severe depression (β = 1.616, 95% CI [0.377, 2.856], P = 0.011).

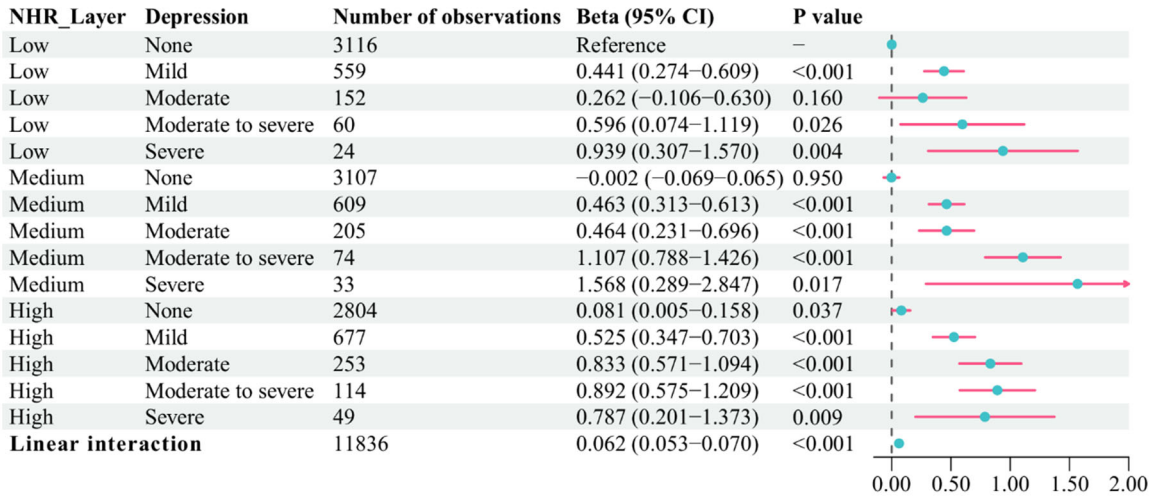

Figure 2. Joint effect analysis of NHR layers and depression grades with OAB score. NHR, neutrophil to high-density lipoprotein cholesterol ratio. 95% CI: 95% confidence interval. Total observations analyzed was 11,836. Joint effect analysis evaluated interaction impacts by creating a new composite categorical variable combining different levels of NHR and depression. This combined variable was analyzed using survey-weighted linear regression, with the baseline joint exposure group serving as reference. Covariates and sampling design adjustments were incorporated throughout the analysis. P-values were derived from Wald tests with design adjusted t-distributions.

Table 3. Associations of depression grades with OAB score stratified by NHR layers.

NHR layer	Depression grades	Number of observations	Beta (95% CI)	*P*-value[a]
Low	None	3116	Reference	—
Low	Mild	559	0.458 (0.297, 0.619)	<0.001
Low	Moderate	152	0.280 (-0.073, 0.633)	0.118
Low	Moderate to severe	60	0.622 (0.097, 1.147)	0.021
Low	Severe	24	0.966 (0.328, 1.604)	0.003
Medium	None	3107	Reference	—
Medium	Mild	609	0.470 (0.315, 0.624)	<0.001

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Medium	Moderate	205	0.473 (0.252, 0.693)	<0.001
Medium	Moderate to severe	74	1.101 (0.794, 1.407)	<0.001
Medium	Severe	33	1.616 (0.377, 2.856)	0.011
High	None	2804	Reference	—
High	Mild	677	0.428 (0.269, 0.587)	<0.001
High	Moderate	253	0.722 (0.469, 0.975)	<0.001
High	Moderate to severe	114	0.814 (0.507, 1.122)	<0.001
High	Severe	49	0.699 (0.103, 1.294)	0.022

a. Fully adjusted model: adjusted for adjusted for age, gender, race, education level, marital status, poverty status, eGFR, smoking, alcohol consumption, hypertension, cardiovascular diseases, diabetes and stroke. Depression grades were stratified by PHQ-9 score. OR, odds ratio. 95% CI: 95% confidence interval. NHR, neutrophil to high-density lipoprotein cholesterol ratio. PHQ-9, patient health questionnaire-9. OAB, overactive bladder. Total observations analyzed was 11,836. Subgroup analysis estimated the effect of depression grades on OAB score within each NHR layer using complex survey-weighted linear regression adjusted for covariates and sampling design. P-values were derived from Wald tests with design-adjusted t-distributions.

3.3. RCS Analysis

We further employed RCS curves to assess the potential nonlinear relationship between each exposure and OAB score (Figure 3). The results suggested as exposure levels or doses increased, OAB score tended to increase as well. Specifically, no significant nonlinear relationships were found between CKM stage (P = 0.811) or NHR (P = 0.384) and OAB score, indicating approximately linear correlations. In contrast, PHQ-9 score exhibited a significant nonlinear relationship with OAB score (P < 0.001), characterized by a steeper positive correlation at lower PHQ-9 scores that slightly flattened at higher scores.

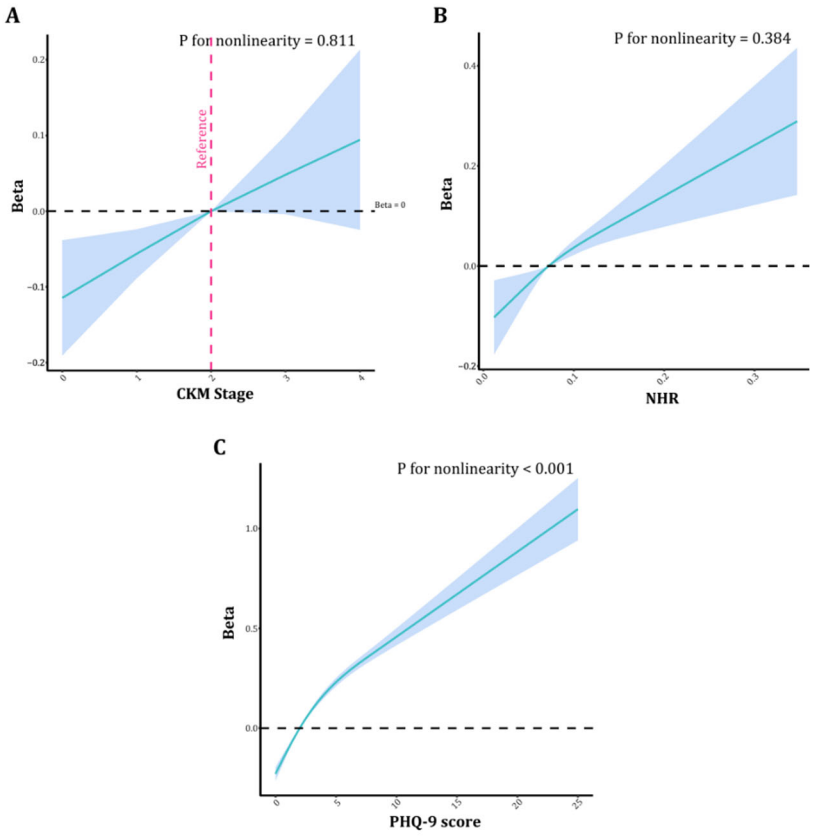

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Figure 3. Restricted cubic spline analysis of CKM stage, NHR and PHQ-9 score with OAB score. (A) RCS analysis of CKM stage on OAB score. (B) RCS analysis of NHR on OAB score. (C) RCS 0 analysis of PHQ-9 score on OAB score. CKM, cardiovascular-kidney-metabolic syndrome. NHR, 1 neutrophil to high-density lipoprotein cholesterol ratio. PHQ-9, patient health questionnaire-9. OAB, overactive bladder. Total observations analyzed was 11,836.

3.4. Mediation Analysis

Given the positive associations observed previously, mediation analyses were conducted to assess whether NHR and PHQ-9 score mediated the association between CKM stage and OAB score (Figure 4). The total effect of CKM stage on OAB score was significant (β = 0.054, 95% CI [0.020, 0.087], P = 0.006). NHR mediated 25.5% of the total effect, with a direct effect of β = 0.040 (95% CI [0.005, 0.073], P = 0.026) and an indirect effect of β = 0.014 (95% CI [0.006, 0.023], P = 0.002). PHQ-9 score mediated 18.1% of the total effect, with a direct effect of β = 0.044 (95% CI [0.010, 0.077], P = 0.012) and an indirect effect of β = 0.010 (95% CI [0.001, 0.018], P = 0.028). The interaction between NHR and PHQ-9 score also showed a significant indirect effect (β = 0.010, 95% CI [0.002, 0.019], P = 0.020), accounting for 18.9% of the total effect. These findings indicate NHR, PHQ-9 score, and their interaction all serve as mediating factors in the relationship between CKM stage and OAB score. However, these analyses are based on cross-sectional data, and therefore results should not be interpreted as implying causation but rather as evidence of associations.

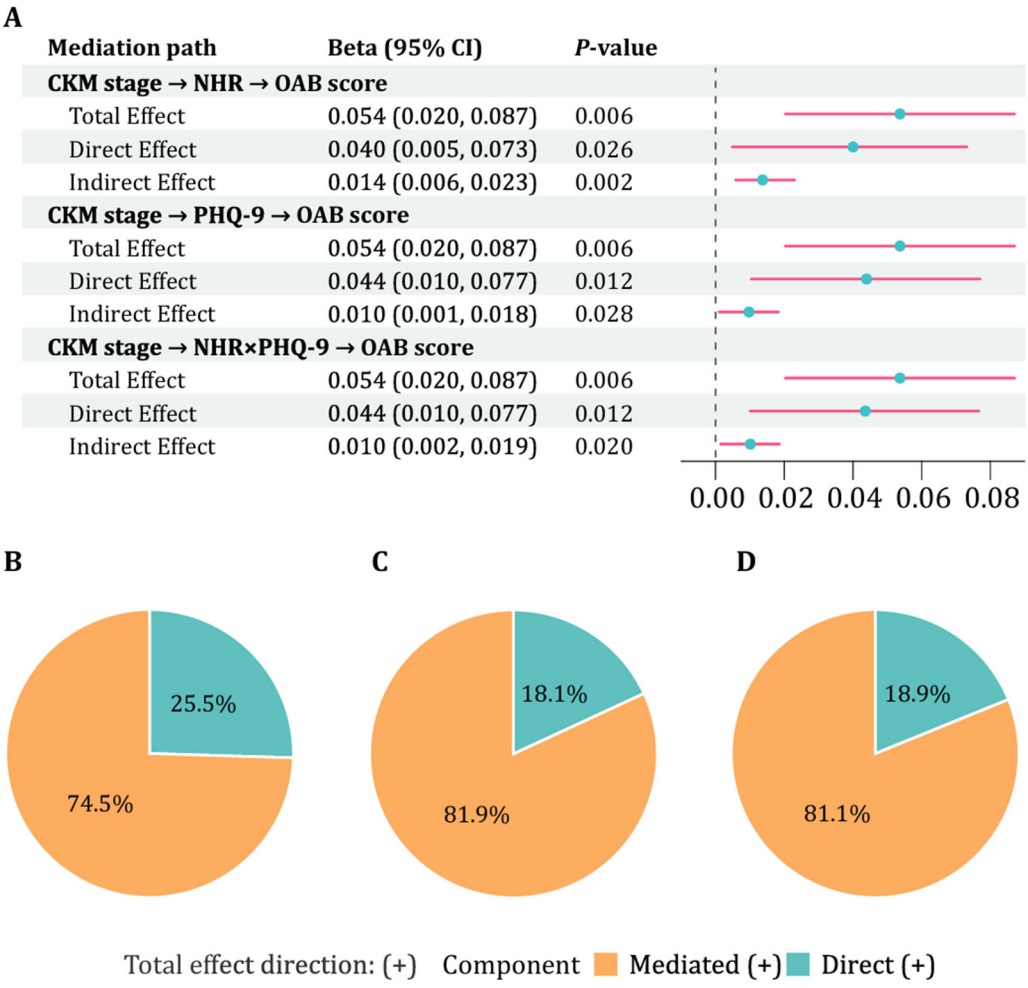

Figure 4. Mediation analysis of CKM stage effect on OAB score via NHR, PHQ-9 score and their interaction. (A) Forest plot for total effect, direct effect and indirect effect for three mediation paths. Mediated proportions are displayed for (B) NHR, (C) PHQ-9 score and (D) NHR×PHQ-9 score. CKM, cardiovascular-kidney-metabolic

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syndrome. NHR, neutrophil to high-density lipoprotein cholesterol ratio. PHQ-9, patient health questionnaire-9. OAB, overactive bladder. Total observations analyzed was 11,836.

3.5. Metabolomic Signatures Associated with OAB

Having revealed the mechanisms lying under the interaction between CKM and OAB, we investigated whether shared metabolomic factors may serve as common modulators of both conditions. Through MR analyses on GWAS datasets of 1,400, 233, and 486 metabolite phenotypes, we identified a series of metabolic signatures that causally influence OAB risk (Figure 5). Genetically predicted lipid-related traits constituted a predominant cluster of risk factors. Specifically, triglyceride and cholesterol measures across multiple lipoprotein subclasses, along with diverse phospholipids (such as 1-linoleoyl-GPE, 1-stearoyl-GPG, phosphoethanolamine, and glycerophosphoinositol species) and sphingomyelins exhibited causal effects on OAB. Fatty acid metabolites were also extensively implicated, spanning saturated, monounsaturated, and long-chain polyunsaturated fatty acids. We observed both positive and negative associations, suggesting that OAB risk is modulated by complex, non-uniform alterations in lipid profiles rather than a unidirectional shift.

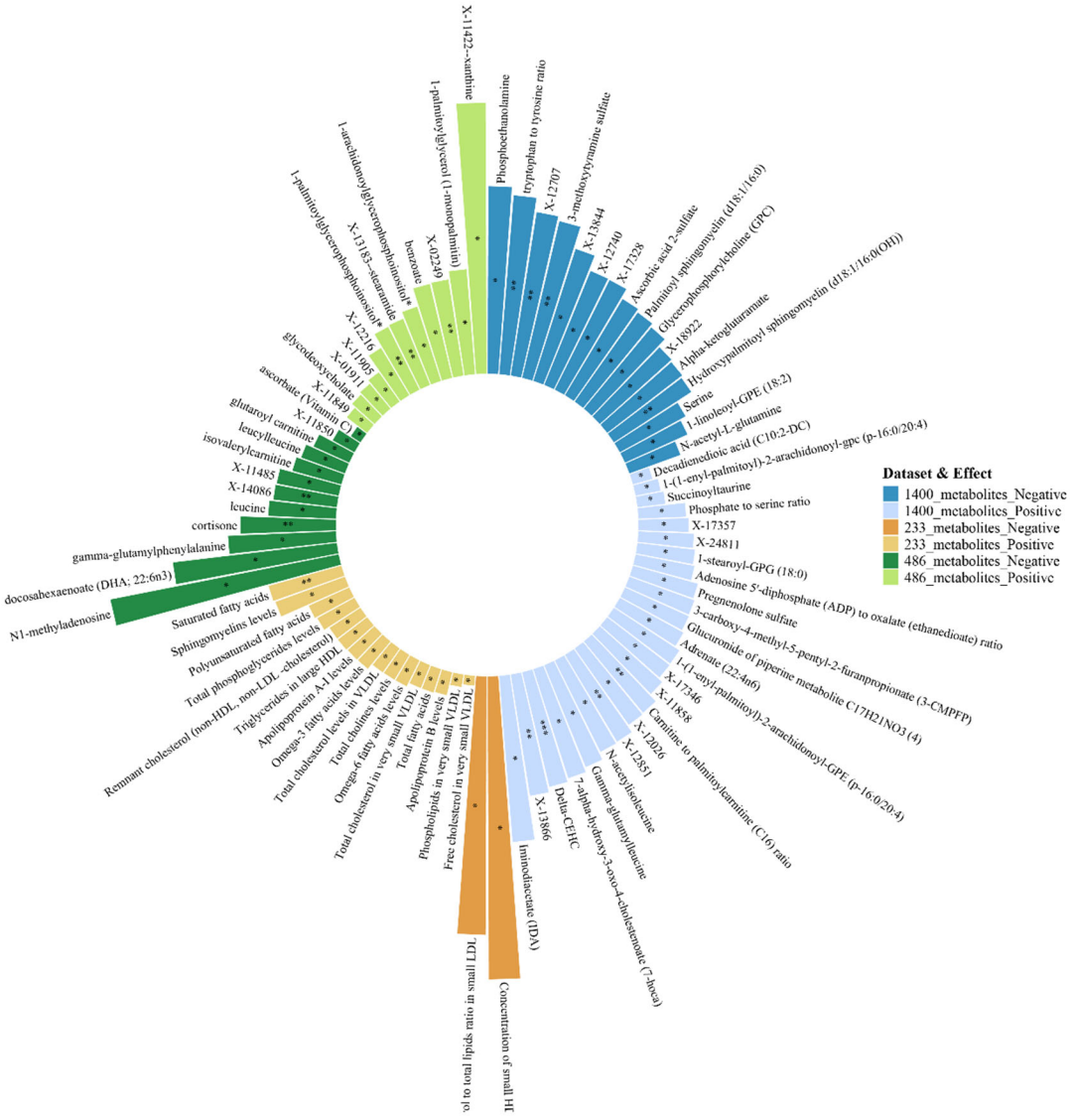

Figure 5. Mendelian randomization analysis of metabolites' causal effect on OAB. Within each dataset, the deep color stands for protective effect (OR1) leading to higher outcome risk.

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Beyond lipid metabolism, genetically determined levels of multiple amino acid-related metabolites were found to influence OAB. Key identifications included branched-chain and aromatic amino acids, gamma-glutamyl peptides, and specific metabolic ratios such as tryptophan to tyrosine. Causal associations were also established for amino acid derivatives, including serine, alpha-ketoglutaramate, and N-acetylisoleucine. Furthermore, metabolites involved in energy metabolism were identified as causal determinants, characterized by significant estimates for organic acids such as isovalerylcarnitine, glutaroylcarnitine, and succinoyltaurine.

Distinct causal effects were also observed for bile acid metabolites, such as glycodeoxycholate and 7-HOCA, as well as steroid-related metabolites including cortisone and pregnenolone sulfate. Redox balance appeared to play a modulatory role, with significant associations identified for ascorbic acid 2-sulfate, ascorbate, and vitamin E metabolites like delta-CEHC. Additionally, nucleoside derivatives (e.g., N1-methyladenosine, xanthine), the dopamine metabolite 3-methoxytyramine sulfate, and several unannotated small molecules (X-series) were implicated as potential risk factors.

Collectively, these findings demonstrate that a systemic metabolomic signature—spanning interconnected domains including lipid, fatty acid, amino acid, bile acid, energy, and redox-related pathways—causally impacts OAB susceptibility. Causal estimates for OAB and other CKM-related outcomes, including CVD, CKD, diabetes, and depression, are presented in Supplementary Figures 1-5.

3.6. Shared Metabolic Patterns Across Multiple Outcomes

To explore metabolic features shared between OAB and other conditions, we performed an overlap analysis using the 1,400-metabolite panel (Figure 6). The largest groups of metabolites were unique to single diseases, meaning they were associated with only one condition. However, overlaps were also present. Metabolites linked to OAB were not limited to a specific OAB-only group. Instead, they appeared in shared groups with CKD, CVD, diabetes, and sometimes depression.

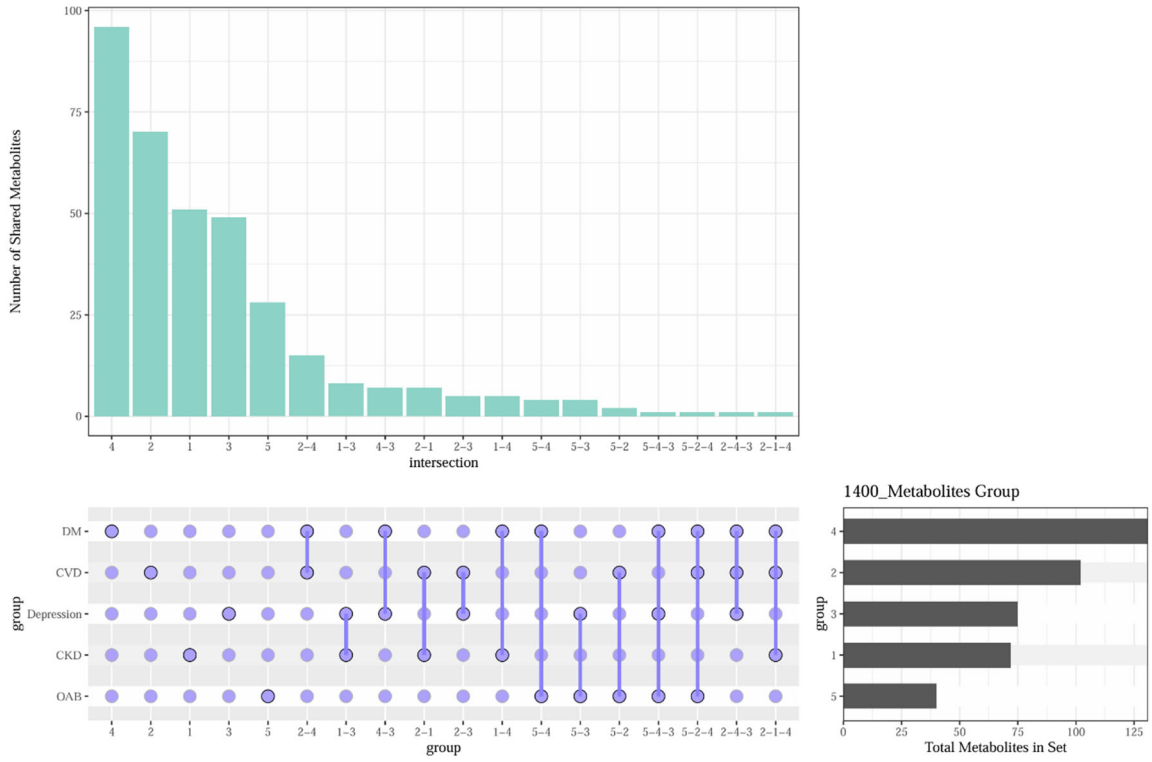

Figure 6. Upset plot for the intersection of metabolites causally affecting different disease risks. The top panel displays the number of shared metabolites across the disease groups. The matrix below shows which groups contribute to each intersection. The right panel shows the total number of metabolites within each individual

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disease group: (1) Diabetes mellitus (DM), (2) Cardiovascular disease (CVD), (3) Depression, (4) Chronic kidney disease (CKD), and (5) Overactive bladder (OAB).

Details of these shared metabolites are listed in Supplementary Table 2. We found that lipids and phospholipids were commonly shared between OAB and other outcomes. Several lipid and phospholipid related metabolites were shared between OAB and other outcomes. These included multiple glycerophospholipids such as plasmalogen and phosphatidylcholine species, as well as sphingolipid related metabolites. For these shared metabolites, the results were mixed: the associations could be positive or negative depending on the specific disease.

Amino acid-related metabolites also appeared in the shared groups. These included serine, gamma-glutamyl peptides, and amino acid ratios, which were shared mainly with depression or cardiometabolic conditions. Additionally, we found intersections involving bile acid related metabolites, steroids, nucleosides, and organic acids.

Overall, the metabolites shared with OAB covered many different biochemical types and were mostly found in combination with cardiometabolic diseases. This suggests that OAB shares common metabolic links with these conditions rather than having a completely isolated metabolic profile. Similar plots and tables for the 486 and 233 metabolite panels are provided in Supplementary Figures 6-7 and Supplementary Tables 3-4.

4. Discussion

In this study, we systematically examined the associations of CKM stage, systemic inflammation, depressive symptoms, and metabolomic profiles with OAB. The results showed that CKM stage, NHR, and PHQ-9 score were each independently associated with OAB severity, with a significant interaction observed between inflammatory and psychological factors. In addition, metabolomic analyses indicated that OAB-related metabolic alterations were not isolated but overlapped with those observed in other CKM-related outcomes.

We employed three regression models to assess the associations of CKM stage, NHR, and PHQ-9 score with OAB score, adjusting for relevant confounders. Subgroup analyses based on NHR levels evaluated the impact of depression severity on OAB score, revealing an interaction between inflammation and psychological status. Interaction analysis further showed that the combined effect of NHR and depression significantly increased OAB risk. Restricted cubic spline analysis identified nonlinear relationships between CKM, NHR, PHQ-9, and OAB. Finally, both inflammatory and psychological factors played critical mediating roles in the pathway through which CKM influences OAB, with an additional synergistic interaction effect enhancing this relationship.

Previous studies have indicated a link between CKM and an increased risk of depression.[15] Our logistic regression analysis based on existing data showed that with advancing CKM stages, the risk of developing OAB significantly increased, which was consistent across all models. These findings suggest that targeted interventions at different stages of CKM syndrome may help prevent or delay its progression, while also reducing the risk of OAB, leading to more effective disease management.

In all models, both NHR and PHQ-9 score were positively correlated with OAB ($P < 0.001$), indicating that inflammation levels and depressive symptoms are important independent contributors to OAB severity.

More importantly, NHR-stratified subgroup analysis demonstrated that the association between depression and OAB was most robust and consistent among individuals with moderate NHR levels, whereas this relationship appeared less stable in those with low or high NHR. This could suggest moderate levels of inflammation may “amplify” the effect of depressive symptoms on OAB. At extremely high levels of inflammation, individuals may have already experienced more complex systemic pathological burdens, masking or diluting the marginal effect of depression on OAB.[31,32]

The significant interaction between NHR and PHQ-9 score suggests that inflammation and psychological factors may not act independently, but rather influence each other and jointly affect

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bladder function. Existing studies have shown that brain-derived neurotrophic factor (BDNF), an important neurotrophic factor, plays a key role in the neuroregulation of the lower urinary tract, with evidence indicating that it could serve as a potential biomarker for OAB.[33–36] Additionally, BDNF is also implicated in the onset and progression of depression.[37–39] Therefore, depression may potentiate bladder overactivity via neurobiological pathways in individuals with mild inflammation. In contrast, chronic immune activation in high inflammation impairs brain-bladder neuroregulation, exacerbating the depression-bladder dysfunction link.[40] This finding provides a new perspective on the complex mechanisms of OAB, suggesting that OAB is not merely a urinary system issue but rather the result of an interplay of biological, psychological, and social factors.

Further mediation analysis supports the indirect effects of CKM on OAB risk through these two pathways (NHR and depression). The progression of CKM may lead to increased systemic inflammation, which not only impacts lower urinary tract function directly but may also trigger OAB symptoms indirectly by affecting brain-mediated emotional regulation and autonomic nervous system function.[41,42] Importantly, the mediation proportion of the interaction between NHR and PHQ-9 score falls between the proportions of NHR and PHQ-9 score solely. This observation can be explained by several factors: First, the interaction term integrates the combined influence of NHR and PHQ-9, which may moderate their individual mediating effects, resulting in a mediation effect that is neither as pronounced as NHR nor as attenuated as PHQ-9 score alone.[43] Second, when inflammation and depression co-occur, they may activate shared physiological mechanisms, which may exhibit diminishing returns, resulting in a combined effect that does not lead to an amplification of the individual influences, thereby contributing to a mediation effect that lies between the individual effects of the two variables.[44] Additionally, other unmeasured or inadequately controlled factors may influence the mediating roles of NHR, PHQ-9, and their interaction, further contributing to the observed intermediate mediation proportion for the interaction term.

The metabolomic findings position OAB within a broader systemic biological framework, implicating generalized metabolic dysregulation across multiple domains rather than isolated biochemical pathway alterations. Causally associated metabolites spanned lipids and lipoproteins, phospholipids, sphingolipids, amino acid derivatives, bile acids, steroids, and redox-related compounds. Previous population based studies have consistently linked dyslipidemia with higher OAB prevalence, suggesting a systemic metabolic burden beyond bladder-specific pathology.[45] Experimental and clinical data further indicate that bile acid and amino acid metabolism modulate visceral sensory signaling and smooth muscle function, both of which are relevant to urinary storage symptoms [46,47]. Notably, many OAB-related metabolites overlapped with those in CKD, CVD, and diabetes, underscoring shared metabolic features aligned with the multisystem nature of CKM syndrome, where metabolic, inflammatory, and vascular disturbances intersect.[48] This shared metabolic background may partly explain the frequent coexistence of OAB with cardiometabolic comorbidities, positioning bladder symptoms as potential downstream manifestations of systemic metabolic stress rather than isolated urological dysfunction.

This study has several notable strengths. Comprehensive adjustment for key covariates, together with restricted cubic spline analysis, subgroup analysis, joint effect analysis, and mediation analysis, enhances the robustness of the observed associations. Importantly, by integrating clinical indicators, psychological measures, inflammatory markers, and metabolomic profiling, this study provides a more comprehensive perspective on OAB than approaches focusing on isolated risk factors. Our findings suggest that OAB is best understood in the context of interacting biological, psychological, and metabolic factors, rather than as a condition driven by a single pathway. In patients with metabolic syndrome, CKD, or CVD, these comorbidities interact to worsen bladder symptoms. The metabolic overlap between OAB and CKM conditions indicates OAB stems from systemic dysregulation, not isolated urological disease. Clinically, effective management may require more than bladder-focused treatment. Addressing cardiometabolic status, inflammation, and psychological health, particularly in CKM patients, could improve outcomes, especially in those with complex metabolic profiles.

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There are some limitations in this study. First, although our study revealed significant associations between CKM, NHR, PHQ-9, and OAB, the cross-sectional nature of the data prevents us from establishing causality between these factors. Future prospective studies or randomized controlled trials will be necessary to confirm the causal relationship between these factors and OAB.

Second, despite adjusting for multiple potential confounders, there may still be unmeasured confounders like genetic background and detailed medication history that could influence the occurrence of OAB. Optimization of the data collection process, by considering additional potential confounding variables, is warranted. Moreover, although this study utilized the large NHANES database, which provides a nationally representative sample, the data primarily comes from the United States, and the findings may vary by region and cultural background. Subsequent researches could validate these results in different regions or racial backgrounds to further enhance the generalizability and applicability of the findings.

5. Conclusions

In conclusion, CKM stage, systemic inflammation, and depressive symptoms independently and interactively associate with OAB severity, linking it to broader cardiometabolic and psychosocial dysregulation. Metabolomic findings further suggest that OAB-related metabolic alterations overlap with those observed in other CKM-related conditions. Our findings provide new insights into early prevention and comprehensive intervention strategies for OAB, suggesting that clinical treatment should integrate the health of the urinary system, inflammatory status, and psychological well-being of patients.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

Author Contributions: Zhechun Wu[†]: Conceptualization and Design, Data Collection, Formal analyses, Writing—Original draft preparation. Yifei Zhang[†]: Conceptualization and Design, Formal analyses, Writing—Original draft preparation. Xuemeng Qiu[†]: Methodology, Data Collection, Writing—Original draft preparation. Jia Zheng: Data Collection, Writing—Original draft preparation, Writing—Reviewing and Editing. Wenyu Shao: Data Collection, Writing—Reviewing and Editing. Yuqing Li: Methodology, Writing—Reviewing and Editing, Supervision. Zhizhi Wang: Methodology, Formal analyses. Zejia Sun: Writing—Reviewing and Editing, Supervision. Wei Wang[*]: Conceptualization, Writing—Reviewing and Editing, Supervision. [†] These authors contributed equally. [*] Corresponding author. All authors read and approved the final manuscript.

Funding: The study was supported by grants from the National Natural Science Foundation of China (No. 82370752) and the Beijing Natural Science Foundation (No. 7252052).

Ethical approval: Ethics approval was obtained from the National Center for Health Statistics Ethics Review Board. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committees, as well as with the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical guidelines.

Informed consent: Informed consent was obtained from all individual participants included in the study. The consent process was carried out according to NHANES protocols, ensuring participants were fully informed about the nature of the study and their rights prior to participation. No personally identifiable information was used in the present study.

Data Availability Statement: The observational data used in this study were publicly available and can be accessed at the NHANES website www.cdc.gov/nchs/nhanes. All GWAS summary statistics used in this work are publicly accessible through the repositories and accession identifiers listed below. GWAS summary statistics for OAB was obtained from the UK Biobank for the phenotype "Bladder: Calcified/Contracted/Overactive" (GWAS ID: ukb-b-373). GWAS summary statistics for CVD, CKD, DM and depression were sourced from the FinnGen consortium release R11 corresponding to the phenotypes FG_CVD(Cardiovascular diseases (excluding rheumatic etc)), N14_CHRONKIDNEYDIS (Chronic kidney disease), T2D (Type 2 diabetes, definitions

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combined), and F5_DEPRESSIO (Depression), respectively, available at https://r11.risteys.finngen.fi/. 1400 blood metabolites: GCST90199621-GCST90201020 in the NHGRI-EBI GWAS Catalog. 486 blood metabolites: the Metabolomics GWAS Server (http://metabolomics.helmholtz-muenchen.de/gwas/). 233 blood metabolites: GCST90301941-GCST90302173 in the NHGRI-EBI GWAS Catalog. All URLs and accession numbers were last verified on 3 September 2025.

Acknowledgments: We sincerely thank all the participants in the National Health and Nutrition Examination Survey and the GWAS research.

Declaration of generative AI and AI-assisted technologies in the writing process: During the preparation of this work the authors used DeepSeek R1 in order to assist with translation and language refinement. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Competing Interests: The authors have no relevant financial or non-financial interests to disclose.

Conflicts of Interest: Authors declare that they have no conflict of interest.

Disclosure Statement: The authors have nothing to disclose.

Abbreviations

CKM	Cardiovascular-kidney-metabolic syndrome
OAB	Overactive bladder
CKD	Chronic kidney disease
PHQ-9	Patient health questionnaire-9
NHR	Neutrophil to high-density lipoprotein cholesterol ratio
NHANES	National Health and Nutrition Examination Survey
NCHS	National Center for Health Statistics
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
AHA	American Heart Association
CVD	Clinical/subclinical cardiovascular disease
KIDGO	Kidney Disease Improving Global Outcomes
eGFR	Estimated glomerular filtration rate
PREVENT	Predicting Risk of CVD EVENTs
UUI	Urge urinary incontinence
OABSS	Overactive bladder symptom score
PIR	Poverty-to-income ratio
CDC	Centers for Disease Control and Prevention
SD	Standard deviation
RCS	Restricted cubic spline
CI	Confidence interval
BDNF	Brain-derived neurotrophic factor

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