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Potential association between magnesium depletion score and hyperuricemia in American adults, a cross-sectional study based on NHANES 2003–2018.

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ABSTRACT

Objective: The pathophysiological mechanisms underlying hyperuricemia necessitate the identification of contributing factors to better understand disease progression and develop effective therapies. This study aimed to investigate the association between Magnesium Depletion Score (MDS) and hyperuricemia.

Methods: A cross-sectional study was sourced from the National Health and Nutrition Examination Survey 2003–2018. Hyperuricemia was defined by serum uric acid levels. MDS was calculated by incorporating factors affecting renal magnesium reabsorption.Weighted multivariable logistic regression was employed to assess the association between MDS and hyperuricemia, with sensitivity analyses to confirm robustness. Additionally, Restricted Cubic Spline (RCS) and Receiver Operating Characteristic (ROC) curve analyses were used to further elucidate the relationship.

Results: Compared to the low MDS group (0–1), the odds ratios (OR) and 95 % confidence intervals (CI) for the middle MDS group (2) and high MDS group (3–5) were 1.76 (1.52–2.04), and 3.14(2.54–3.88), respectively. The RCS analysis illustrated a linear dose-response relationship between MDS and hyperuricemia. The ROC analysis demonstrated that MDS had an area under the curve of 0.720 (95 % CI, 0.717–0.721).

Conclusions: This study highlights a strong association between MDS and hyperuricemia risk, emphasizing the importance of addressing magnesium deficiency in hyperuricemic patients.

1. Introduction

As the end product of purine metabolism, uric acid is primarily excreted by the kidneys, with a smaller portion metabolized by the intestines.(Yanai et al., 2021) Imbalances in uric acid metabolism can lead to elevated uric acid levels in extracellular fluid and serum, progressively resulting in impaired uric acid excretion, a metabolic condition known as hyperuricemia. It is well-established that hyperuricemia affects more than just gout and kidney disorders. Common health conditions, including obesity, cardiovascular disease, diabetes, and metabolic syndrome, have been closely associated with hyperuricemia.(Du et al., 2024) With lifestyle changes, hyperuricemia has become the second most prevalent metabolic disorder after diabetes.(Zhao et al., 2022) Globally, the prevalence of hyperuricemia among adults is estimated to exceed 10 %. According to the National Health and Nutrition Examination Survey (NHANES), nearly 20 % of U.S. adults are affected by hyperuricemia.(Perez-Ruiz et al., 2015; Zhang et al., 2021; Zhu et al., 2012) To gain a deeper understanding of this complex public health issue, further investigation into the pathophysiological mechanisms underlying the prevalence and progression of hyperuricemia is crucial.

Magnesium is a crucial mineral essential for numerous physiological functions. As a cofactor for over 300 enzymatic reactions, magnesium is integral to adenosine triphosphate synthesis, the primary cellular energy currency. Additionally, it facilitates transmembrane transport of essential metal ions, including calcium and potassium, and stabilizes DNA and RNA secondary structures.(Jahnen-Dechent and Ketteler, 2012) Despite its importance, magnesium deficiency is a frequently discussed yet often overlooked health issue. Research indicates that over half of Americans fail to meet the recommended dietary magnesium intake.(Fan et al., 2021; Tarleton, 2018) This may be due to the difficulty in accurately

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detecting magnesium deficiency. Most magnesium is stored in bones, muscles, and other soft tissues, with serum magnesium constituting only 0.3 % of the total body magnesium. Moreover, the body's magnesium balance is meticulously regulated by various factors, including dietary intake, skeletal absorption, intracellular and extracellular exchanges, and renal excretion. Consequently, serum magnesium testing may not be an ideal method for diagnosing magnesium deficiency.(Leenders and Vervloet, 2019) In light of these challenges, Fan et al. proposed the Magnesium Depletion Score (MDS) as a more effective means of identifying magnesium deficiency.(Fan et al., 2021) Validated through the magnesium tolerance test, the MDS has demonstrated superior predictive capability for magnesium deficiency compared to serum magnesium levels, magnesium intake, and urinary magnesium excretion. Recent studies have further confirmed the strong association between MDS and various health conditions, including cardiovascular disease (CVD), frailty syndrome, and chronic obstructive pulmonary disease. The MDS shows promise as a valuable tool for identifying subpopulations at risk of magnesium deficiency.(Song et al., 2024; Wang et al., 2024a,b)

The design of the MDS thoughtfully incorporates prevalent risk factors among Americans, such as alcohol consumption, estimated glomerular filtration rate (eGFR), and the use of certain medications, including diuretics and proton pump inhibitors. These factors are also associated with hyperuricemia and abnormal uric acid metabolism. (Fukui et al., 2024; Sun and Wang, 2024; Yanai et al., 2021; Zhu et al., 2023) Moreover, the metabolic pathways of magnesium and uric acid in the human body exhibit significant similarities. Approximately one-third of uric acid is excreted through the intestines or reabsorbed by the gut microbiota, a process that parallels the intestinal absorption of magnesium. Furthermore, the excretion of both magnesium and uric acid is predominantly regulated by the kidneys, with over 80 % of plasma magnesium undergoing filtration and reabsorption by the renal tubules. (Fan et al., 2021; Yanai et al., 2021)Given this intricate interplay, the severity of magnesium deficiency may also serve as an indicator of the risk for hyperuricemia. Understanding this connection could enhance the assessment and management of conditions related to magnesium deficiency and uric acid metabolism.

Previous studies have suggested a protective effect of increased magnesium intake against hyperuricemia. However, the accuracy of 24-h dietary recalls in reflecting long-term magnesium metabolism is limited.(Zhang and Qiu, 2018) Importantly, large-scale, nationally representative studies examining the association between MDS and hyperuricemia are currently lacking. To address this knowledge gap, we designed a cross-sectional study utilizing data from the NHANES collected between 2003 and 2018. This study aimed to investigate the relationship between MDS and hyperuricemia, potentially elucidating the impact of magnesium deficiency on the risk of developing hyperuricemia.

2. Methods

2.1. Study population

The NHANES is a nationally representative, cross-sectional survey conducted every two years by the Centers for Disease Control and Prevention. It utilizes a stratified, multi-stage sampling design to collect extensive health data through physical examinations, questionnaires, and laboratory tests. Detailed information about the survey, data collection process, and publicly available data files can be found at http://www.cdc.gov/nchs/nhanes.html. This study adhered to the ethical protocols approved by the National Center for Health Statistics Research Ethics Review Board, and no further institutional review was necessary. From an initial dataset of 80,312 participants from NHANES 2003–2018, we employed the following exclusion criteria: **1)** age under 20 years ($n = 35,522$); **2)** pregnancy ($n = 941$); **3)** missing data for MDS calculation (alcohol consumption, serum creatinine, medication use) ($n = 5713$); **4)** missing serum uric acid data ($n = 4503$); and **5)** missing covariates and special weights (Fasting Subsample 2 Year MEC Weight) ($n = 21,093$). This resulted in a final sample of 12,540 participants for analysis (Fig. 1).

2.2. Assessment of MDS

The MDS calculation method, adapted from Fan et al., utilizes data from the NHANES. MDS is determined by a total score derived from four factors: **1)** diuretic use (1 point); **2)** proton pump inhibitor (PPI) use (1 point); **3)** excessive alcohol consumption (men >2 drinks/day, women >1 drink/day, 1 point); and **4)** renal function status, assessed by eGFR. An eGFR of 60–90 mL/min/1.73 m^2 corresponds to 1 point, while <60 mL/min/1.73 m^2 indicates 2 points, reflecting mild and chronic kidney disease, respectively.(Levey et al., 2009) The Chronic Kidney Disease Epidemiology Collaboration equation was used to calculate eGFR. For further analysis, MDS was categorized into three groups: Low (0–1), Middle (2), and High (3–5).

2.3. Assessment of Hyperuricemia

Uric acid, oxidized by uricase to allantoin and hydrogen peroxide, was measured using either the Beckman UniCel® DxC800 Synchron or the Beckman Synchron LX20 (Beckman Coulter, Inc., Brea, CA, USA). Hyperuricemia was defined based on serum uric acid levels: ≥420 μmol/L for males and ≥ 360 μmol/L for females.(Feig et al., 2008)

2.4. Potential Covariates

The covariates included in this study were primarily selected based on published literature and clinical practice, and were categorized into three groups: demographic and behavioral health characteristics, disease status, and nutritional intake. Demographic and behavioral factors included age, gender, race, education level, marital status, smoking status (determined by serum cotinine levels <3.3 ng/mL and ≥ 3.3 ng/mL), and physical activity level. Body mass index (BMI) was divided into four groups (<18.5, 18.5–24.99, 25–29.99, ≥30).

Disease status was assessed through a combination of questionnaire data and laboratory measurements, including hypertension, diabetes, coronary heart disease (CHD), stroke, cancer and chronic kidney diseases (CKD). Hypertension diagnosis was based on average blood pressure measurements, as well as self-reported hypertension history and medication use. Diabetes diagnosis was determined by both self-reported history and glycated hemoglobin levels (<6.5 % and ≥ 6.5 %). Diagnoses of other diseases were obtained from questionnaires.

Nutritional intake was calculated from the average of two 24-h dietary recalls, encompassing several nutrients and magnesium intake. Additionally, serum albumin levels were included as a marker of nutritional status. For a detailed overview of the included variables and classification methods in this study is presented in Table 1. The cleaned datasets are provided in supplementary material 1.

2.5. Statistical analysis

NHANES employs a complex sampling design and assigns specific weights to each participant's data. To accurately analyze this dataset, we adhered to NHANES's recommended weighting and stratification methods, incorporating these weights into our statistical analyses. Categorical variables are presented as unweighted frequencies and weighted percentages. The chi-square test was used to assess differences between groups for categorical variables. For continuous variables, if they conform to normal distribution after verifying normality, ANOVA is used and expressed as mean ± Standard Error. Otherwise, the median (interquartile range) values were reported, and the Wilcoxon signed-rank test was used to compare group differences.

To investigate the association between MDS and hyperuricemia, we employed three weighted logistic regression models. Model 1 served as

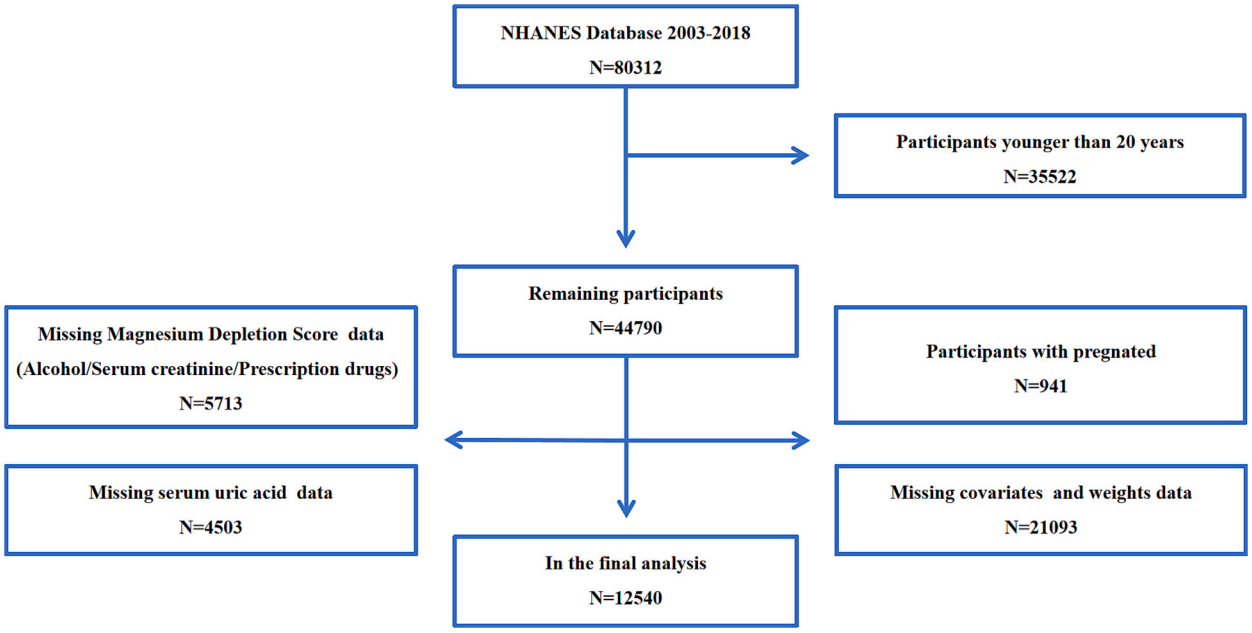

Fig. 1. The flowchart of participants selection from NHANES 2003–2018 among United States adults.
Note: Abbreviations: NHANES: National Health and Nutrition Examination Survey.

the unadjusted model, including no covariates. Model 2 introduced adjustments for demographic characteristics, including age, gender, race, education level, and income. Finally, Model 3 incorporated adjustments for all available covariates. To strengthen the robustness of our findings, we conducted sensitivity analyses using two approaches. First, we excluded participants with CKD to isolate the effects of MDS on hyperuricemia independent of CKD. Second, we re-ran the models with MDS treated as a categorical variable with six levels (0–5) instead of grouping the categories. These methodological strategies enhance the reliability and interpretability of our results.

To assess the trend relationship between hyperuricemia and MDS across the entire range, we treated the ungrouped MDS score (0–5) as a continuous variable and incorporated it, along with all covariates, into a Restricted Cubic Spline (RCS) model. This approach allowed us to examine the potential non-linear relationship between MDS and hyperuricemia. Furthermore, acknowledging that some factors used in calculating the MDS may also be associated with hyperuricemia, we employed Receiver Operating Characteristic (ROC) analysis to calculate the Area Under the Curve (AUC). This evaluation aimed to determine the effectiveness of MDS as a predictor of hyperuricemia. To enhance the robustness of ROC curves, confidence intervals were calculated for the weighted logistic regression models by bootstrapping methods.

The statistical analysis was performed using two software packages: STATA 17.0 (StataCorp LLC, College Station, Texas, USA) and R software (version 4.2.3; http://www.R-project.org, R Foundation for Statistical Computing, Austria). Two-sided *P* values less than 0.05 were considered statistically significant.

3. Results

3.1. Baseline characteristics

The Table 1 presents the baseline characteristics of the 12,540 participants, including 6191 men and 6349 women. Of these, 2466 individuals (19.7 %) were diagnosed with hyperuricemia. Notably, most variables exhibited significant differences between the hyperuricemia and non-hyperuricemia groups, except poverty-income ratio, activity status and smoking status. Specifically, individuals with hyperuricemia were more likely to be male, older, non-Hispanic White, less educated, and living alone. In terms of health status, the hyperuricemia group had significantly higher rates of obesity and comorbidities compared to the non-hyperuricemia group. The difference between the two groups was further amplified in MDS. The proportion of MDS low (0–1) was about one-third higher in group non-hyperuricemia than in group hyperuricemia (65.9 %,43.0 %). Interestingly, this trend was completely reversed in MDS High (3–5), with nearly three times as many people with MDS High (3–5) in hyperuricemia as in non-hyperuricemia (21.7 %,7.2 %). Regarding nutrient intake, the hyperuricemia group generally had lower nutrient intake compared to the non-hyperuricemia group. Details about the comparison between MDS groups are presented in supplementary material 2.

3.2. Association between MDS and Hyperuricemia

The association between MDS and hyperuricemia is detailed in the logistic regression models presented in Table 2. All three models consistently demonstrated a strong positive correlation. In Model 3, which adjusted for all covariates, individuals in the middle (2) and high MDS groups (3–5) exhibited significantly higher prevalence of hyperuricemia compared to the low MDS group (0–1). The odds ratios (OR) and 95 % confidence intervals (CI) for these groups were 1.76 (1.52–2.04), and 3.14 (2.54–3.88), respectively. Sensitivity analyses, excluding participants with CKD or treating MDS as an ungrouped categorical variable (0–5), yielded robust results. Notably, there was a clear linear increase in hyperuricemia prevalence with increasing MDS. In the highest MDS group (5), the OR (95 % CI) for hyperuricemia was 32.26 (11.05–94.20). Meanwhile, test for trend showed that there was an obvious linear relationship between the two in different populations (*P* for trend <0.001). Additionally, participants with obesity, hypertension, and CKD had an elevated risk of hyperuricemia, with OR (95 % CI) of 9.66 (3.92–23.84), 1.88 (1.63–2.18), and 1.49 (1.10–2.01), respectively. Females exhibited a 30 % lower risk of hyperuricemia compared to males (OR (95 % CI): 0.73 (0.63–0.86)). Further details are available in the supplementary material 2.

3.3. RCS and ROC curves

The RCS curve demonstrated a linear dose-response relationship

Table 1
Distribution of selected characteristics of the United States adults from NHANES 2003–2018. (N = 12,540).

Characteristics	Overall (N = 12,540)	Non-Hyperuricemia (N = 10,074)	Hyperuricemia (N = 2466)	*P value
Gender, N (%)				<0.001
Male	6191(48.8)	4870(49.3)	1321(55.3)	
Female	6349(51.2)	5204(52.7)	1145(44.7)	
Age, N (%)	50(35,64)	48 (34, 62)	57 (41, 69)	<0.001
20–50	6431(57.5)	5492(60.1)	939(46.5)	
>50	6109(42.5)	4582(39.9)	1527(53.5)	
Race/ethnicity, N (%)				<0.001
Mexican American	1886(7.4)	1630(8.0)	256(4.9)	
Other Hispanic	1024(4.5)	876(4.8)	148(3.3)	
Non-Hispanic White	5980(71.2)	4735(70.6)	1245(73.8)	
Non-Hispanic Black	2500(10.4)	1922(10.1)	578(11.5)	
Other Race	1150(6.5)	911(6.4)	239(6.6)	
Education level, N (%)				<0.001
Less than high school	5648(37.3)	4518(37.1)	1130(38.3)	
High school or equivalent	3808(31.8)	3006(31.2)	802(34.6)	
More than high school	3084(30.9)	2550(31.7)	534(27.7)	
Marital status, N (%)				<0.001
Married/Living with partner	7670(65.0)	6199(65.4)	1471(63.2)	
Divorced/ Separated/ Widowed	2698(17.7)	2066(16.8)	632(21.2)	
Never married	2172(17.3)	1809(17.7)	363(15.6)	
Poverty to income ratio, N (%)				0.447
≤1.30	3580(19.2)	2901(19.5)	679(18.3)	
1.31–3.50	4888(37.0)	3910(36.9)	978(37.7)	
>3.50	4072(43.7)	3263(43.7)	809(44.0)	
Body mass index, N (%)				<0.001
<18.50	175(1.3)	165(1.5)	10(0.2)	
18.50–24.99	3436(29.0)	3121(33.0)	315(11.7)	
25.00–29.99	4184(33.0)	3448(33.5)	736(30.9)	
≥30.00	4745(36.7)	3340(32.0)	1405(57.2)	
Activities status, N (%)				0.142
Inactive	6542(47.3)	5231(47.2)	1311(47.9)	
Moderate	3126(26.8)	2496(26.6)	630(27.9)	
Vigorous	602(5.0)	493(5.1)	109(4.3)	
Both	2270(20.9)	1854(21.6)	416(19.9)	
Smoking status, N (%)				0.532
No	9290(73.9)	7418(73.7)	1872(74.3)	
Yes	3250(26.2)	2656(26.3)	594(25.6)	
Hypertension, N (%)				<0.001
No	7080(61.8)	6212(66.8)	868(40.3)	
Yes	5460(33.2)	3862(33.2)	1598(59.7)	
Diabetes, N (%)				<0.001
No	10,654(89.5)	8727(90.8)	1927(84.1)	
Yes	1886(10.5)	1347(9.2)	539(15.9)	
Stroke, N (%)				<0.001
No	10,275(97.3)	9760(97.7)	2315(95.4)	
Yes	465(2.8)	314(2.3)	151(4.6)	
Coronary heart disease, N (%)				<0.001
No	11,992(96.4)	9697(96.9)	2295(94.3)	
Yes	548(3.6)	377(3.1)	171(5.7)	
Chronic kidney disease, N (%)				<0.001
No	12,160(97.9)	9845(98.4)	2315(95.9)	
Yes	380(2.1)	229(1.6)	151(4.1)	
Cancer, N (%)				<0.001
No	11,333(90.5)	9179(91.1)	2154(87.9)	
Yes	1207(9.5)	895(8.9)	312(12.1)	
Energy intake (kcal/day, median (IQR))	1927 (1482.0, 2487.5)	1946.5 (1502.9, 2504.0)	1844.3 (1402.5, 2424.3)	<0.001
Protein intake (g/day, median (IQR))	75.3 (56.3, 97.9)	75.6(56.7, 98.1)	74.1(54.9, 97.0)	0.037
Carbohydrate intake (g/day, median (IQR))	232 (175.3, 302.6)	236.3 (179.3, 305.9)	213.7 (162.9, 286.7)	<0.001
Magnesium intake (mg/ day, median (IQR))	267 (203.5352.0)	270.5(206.5, 355.5)	255.0 (192.9, 337.5)	<0.001
Albumin (g/L, median (IQR))	42 (40.0, 44.0)	42(40.0, 44.0)	42 (40.0, 44.0)	0.002

Note: Unweighted number (weighted percentage) for categorical variables: *P value was calculated by weighted chi-square test.
Median (IQR) for continuous variables: *P value was calculated by Wilcoxon signed-rank test. $P < 0.05$ was considered.
Abbreviations: IQR: InterQuartile range; NHANES: National Health and Nutrition Examination Survey.

Table 2
Multiple logistic regression analyses between MDS and Hyperuricemia in the United States adults from NHANES 2003–2018.

MDS	No.	Model 1 OR (95 % CI)	Model 2 OR (95 % CI)	Model 3 OR (95 % CI)
Low (0–1)	7739	1.00(Reference)	1.00(Reference)	1.00(Reference)
Middle (2)	3395	2.01(1.76 to 2.31)	1.96(1.70 to 2.26)	1.76(1.52 to 2.04)
High (3–5)	1406	4.63(3.96 to 5.41)	4.26(3.54 to 5.14)	3.14(2.54 to 3.88)
*P for trend		<0.001	<0.001	<0.001

Note: Model 1: unadjusted.
Model 2: adjusted for age, gender, race, education level, marital status and poverty to income ratio.
Model 3: adjusted all covariates, including that age, gender, race, education level, marital status and poverty to income ratio, body mass index, activities status, smoking status, hypertension, diabetes, stroke, coronary heart disease, chronic kidney disease, cancer, energy intake, protein intake, carbohydrate intake, magnesium intake, and serum albumin. *P value calculated by Student's t-test.
Abbreviations: MDS: Magnesium Depletion Score; OR: Odds Ratio; CI: Confidence Interva. NHANES: National Health and Nutrition Examination Survey.

between the ungrouped MDS (0–5) and hyperuricemia (P for overall <0.001, P for nonlinear = 0.843) (Fig. 2A). This finding aligned closely with the results obtained from the logistic regression analysis. Additionally, the ROC curve analysis revealed an AUC of 0.720 (95 % CI, 0.717–0.721) for the MDS, suggesting its predictive ability for hyperuricemia (Fig. 2B).

4. Discussion

The findings of this study demonstrated a significant positive association between increasing MDS and the risk of hyperuricemia. This association persisted even after adjusting for various covariates, including demographic characteristics, behavioral health factors, disease conditions, and nutritional intake. Both multiple logistic regression analyses and RCS curves supported this relationship. Sensitivity analyses

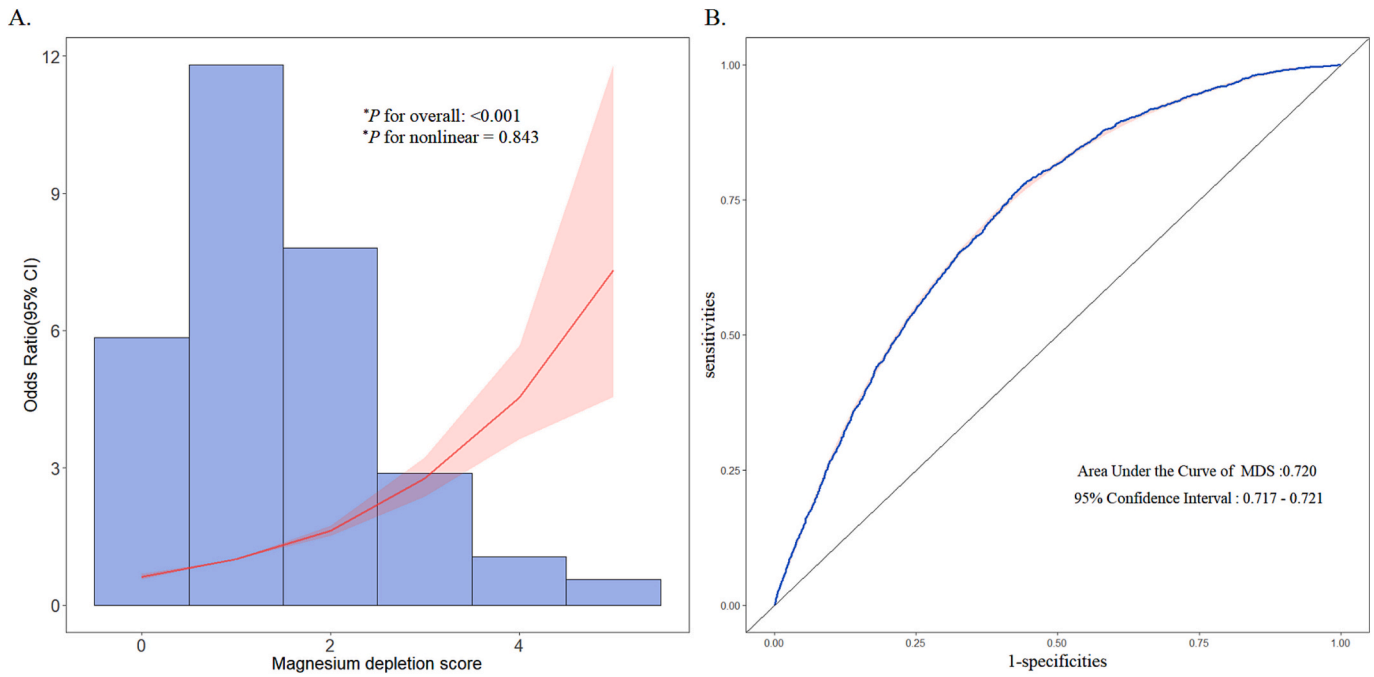

Fig. 2. RCS curve and ROC curve of the relationship between MDS and Hyperuricemia in the United States adults from NHANES 2003–2018.
Note: (A)RCS curve. *P:P value calculated by likelihood ratio test.
(B)ROC curve. Both models adjusted for all covariates, including that age, gender, race, education level, marital status and poverty to income ratio, body mass index, activities status, smoking status, hypertension, diabetes, stroke, coronary heart disease, chronic kidney disease, cancer, energy intake, protein intake, carbohydrate intake, magnesium intake and serum albumin.
Abbreviations: RCS: Restricted cubic spline; ROC: Receiver operating characteristic; MDS: Magnesium depletion score; CI: Confidence intervals. AUC: Area under the curve.

further confirmed the robustness of these findings. Moreover, the ROC curve analysis revealed a moderate predictive ability of MDS for hyperuricemia risk, with an AUC of 0.720. These results highlight the importance of magnesium deficiency in the context of hyperuricemia risk among American adults. While the specific mechanisms linking MDS, magnesium deficiency, and hyperuricemia remain unclear, plausible mechanisms can be hypothesized based on existing literature.

One primary argument linking magnesium deficiency to hyperuricemia centers on their opposing effects on inflammation. Uric acid, at physiological level, exhibits anti-inflammatory and antioxidant properties, protecting neuronal cells and inhibiting apoptosis. However, at elevated levels, uric acid can exacerbate oxidative stress and transform into pro-inflammatory and pro-oxidative molecules.(Du et al., 2024) High-sensitivity C-reactive protein (hs-CRP) and C-reactive protein (CRP) are key markers of systemic inflammation. In hyperuricemia, soluble uric acid can promote low-density lipoprotein oxidation, induce lipid peroxidation, and elevate CRP levels, intensifying vascular inflammation and oxidative stress.(Choi et al., 2014) Moreover, hs-CRP can further compromise vascular endothelial cells by activating the complement system.(Ciarambino et al., 2022) Magnesium is well-known for its potent anti-inflammatory properties. Magnesium deficiency is often associated with increased CRP levels, which can be alleviated through magnesium supplementation.(Maier et al., 2021; Nielsen, 2018) For instance, Yang et al. demonstrated that a combination of compound Danshen injection and magnesium sulfate significantly reduced serum myeloperoxidase and hs-CRP levels in patients with severe preeclampsia, compared to a control group.Additionally, recent studies have proposed that serum uric acid to creatinine ratio(SUA/sCr) could serve as a predictor of preeclampsia, with higher SUA/sCr levels often indicating adverse pregnancy outcomes. The opposing effects of magnesium supplementation and elevated SUA on eclampsia may help confirm this potential association.(Yang et al., 2018) (Dal et al., 2024; Piani et al., 2023)Another study suggested that magnesium supplementation may benefit patients with hypothyroidism and hyperthyroidism-related conditions by reducing hs-CRP levels.(Rabbani et al., 2021) Therefore, maintaining adequate magnesium levels may be a valuable strategy to mitigate inflammation in the progression of hyperuricemia. We hypothesize that this effect is mediated through magnesium's ability to inhibit inflammatory signaling pathways and protect vascular endothelial function.Research suggests that uric acid can bind to Toll-like receptors (TLRs), triggering an inflammatory response. Uric acid crystals, through their interaction with various receptors, activate the nuclear factor-kappa B (NF-κB) signaling pathway, leading to increased transcription of inflammatory proteins.(Chen et al., 2024; Cheng et al., 2020; Du et al., 2024) Gong et al. demonstrated that magnesium isoglycyrrhizinate, a magnesium salt of the 18α-glycyrrhizin stereoisomer, inhibits the lipopolysaccharide /TLRs/NF-κB signaling pathway, significantly reducing the expression of tumor necrosis factor-alpha, interleukin-6, TLR2, TLR4, and NF-κB mRNA.(Gong et al., 2022) Therefore, suppressing inflammation may be a crucial mechanism by which magnesium reduces the risk of hyperuricemia. As magnesium deficiency worsens, the risk of developing hyperuricemia increases.

The kidneys play a crucial role in the reabsorption and excretion of magnesium and uric acid. When kidney function is impaired, metabolic imbalances in uric acid and magnesium may further exacerbate renal damage. In recent years, the bidirectional relationship between hyperuricemia and CKD has been frequently discussed. Studies suggest that hyperuricemia may act as a precursor for CKD development, promoting its onset and progression through mechanisms such as vascular smooth muscle cell proliferation and endothelial dysfunction. Conversely, the pathological progression of CKD reduces uric acid excretion, leading to hyperuricemia and worsening pre-existing renal damage. However, most Mendelian randomization studies have failed to establish a causal relationship between uric acid and CKD, which may be attributed to the combined effects of ethnicity, dietary habits, and genetic factors. (Bonino et al., 2020; Manganaro, 2024)Of note, according to the MDS

criteria, patients with moderate to severe CKD (eGFR <60 mL/min/1.73 m^2) are more likely to exhibit a high MDS, which partially reflects the degree of magnesium deficiency. Thus, the role of magnesium deficiency in CKD should not be overlooked. Diabetic kidney disease (DKD) is widely recognized as a classic model for studying CKD. A retrospective study revealed that lower serum magnesium levels are a risk factor for reduced eGFR and the presence of microalbuminuria or overt proteinuria in DKD patients, and are associated with an increased risk of DKD progression. (Yanagawa et al., 2021)This suggests that magnesium deficiency may predict CKD onset and accelerate its progression. Similarly to hyperuricemia, the progression of CKD also exacerbates magnesium deficiency. Interestingly, acute kidney injury (AKI), such as that caused by diabetic ketoacidosis (DKA), often results from prerenal factors like dehydration. This type of AKI can impair renal tubular function, particularly in the proximal tubules, leading to metabolic disturbances in uric acid and magnesium. The difference is, DKD involves progressive and irreversible kidney damage, whereas the acute kidney injury caused by DKA may be reversible after correcting dehydration and acidosis. (Ding et al., 2024; Melena et al., 2022)A positive association between MDS and kidney stone risk may be due to magnesium's role in inhibiting calcium oxalate crystal formation.(Xu et al., 2024) Uric acid levels are positively correlated with kidney stone risk, as uric acid crystals can significantly induce the development of calcium oxalate monohydrate crystals.(Ando et al., 2021; Grases et al., 2007) Tubular dysfunction and interstitial fibrosis in CKD impair magnesium reabsorption, leading to hypomagnesemia and potentially accelerating CKD progression. (Sakaguchi, 2022) In conclusion, magnesium may regulate serum uric acid levels through anti-inflammatory effects, reduced kidney disease risk, and other potential mechanisms. Disruption of this balance due to magnesium deficiency significantly increases the risk of hyperuricemia. The proposed mechanisms support our research findings, though further investigation is needed to confirm certain speculations and hypotheses.

The ROC curve indicates that MDS has predictive potential for the risk of hyperuricemia. This may be because the factors used to calculate MDS also influence the risk of hyperuricemia. Excessive alcohol consumption and impaired renal function are well-known risk factors for hyperuricemia. The mechanism of diuretic-induced hyperuricemia is unclear, likely due to the diverse types of diuretics with distinct mechanisms of action. For example, hydrochlorothiazide may enhance serum uric acid reabsorption while inhibiting excretion. Yuko et al. identified single nucleotide polymorphisms associated with increased serum uric acid levels following indapamide treatment. Further functional investigations are needed to elucidate their specific roles. Diuretic-induced hyperuricemia is likely a result of multiple interacting factors, with the association between hyperuricemia and poorer prognosis potentially stemming from the progression of other comorbid conditions. When multiple diseases are intertwined, it becomes increasingly challenging to delineate the mechanisms at play. Nonetheless, numerous studies indicate that diuretic-related hyperuricemia is a significant risk factor for disease progression and prognosis, particularly among patients requiring long-term diuretic therapy for CVD.(Chenaghlou et al., 2024; Maloberti et al., 2021; Ohta et al., 2020) Regarding PPIs, while there is limited literature on their impact on hyperuricemia, we speculate that it may involve indirect genetic regulation. ATP-binding cassette subfamily G member 2(ABCG2)/breast cancer resistance protein (BCRP), localized in renal tubules and intestinal epithelial cells, promotes uric acid excretion. A specific ABCG2 polymorphism (rs2231142) reduces uric acid excretion activity, increasing susceptibility to hyperuricemia and gout.(Chen et al., 2021; Horváthová et al., 2019) PPIs, while intended to protect against gastrointestinal bleeding, have been associated with bleeding complications, possibly due to their role as ABCG2 inhibitors. Additionally, alterations in gut microbiota due to PPI use may impact uric acid metabolism. While existing literature provides some explanation, more targeted studies are needed to establish definitive causal relationships.

Our study has some strengths. To our knowledge, this is the first study to investigate the association between MDS and hyperuricemia using NHANES data. By adhering to official weight usage guidelines established by the NHANES, our findings can be generalized to a broader population. RCS and ROC curves provide a more comprehensive understanding of the relationship between MDS and hyperuricemia, highlighting the clinical significance of MDS in patients with elevated uric acid levels. Moreover, MDS was selected instead of measuring magnesium intake, given that MDS may more accurately reflect body magnesium deficiency. This choice enhances the robustness of our findings.

This study has several limitations. While MDS is a valuable screening tool, it does not account for factors like genetic susceptibility, autoimmune conditions, or other diseases that may contribute to magnesium deficiency. As a cross-sectional study, our findings demonstrate correlations but cannot establish causal relationships, which requires longitudinal validation. Another significant limitation of this study is the inability to obtain data on the treatment of hyperuricemia or magnesium deficiency in participants, which may impact the observed associations and conclusions. Addressing this limitation would require long-term follow-up and more comprehensive, detailed, and rigorous prospective studies.

5. Conclusion

In summary, our study demonstrates a significant positive correlation between MDS and hyperuricemia risk in the U.S. population. This association was consistent across various age and gender groups. Additionally, MDS shows promise as a novel indicator for predicting hyperuricemia risk. While our study has limitations, future research could benefit from focusing on magnesium levels in hyperuricemia patients. Furthermore, the calculation methods used to assess MDS could be refined to develop a more sensitive and reliable hyperuricemia risk assessment tool.

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Ethical approval and consent to participate

The study protocol for the US NHANES was approved by the US NHANES institutional review board and National Center for Health Statistics Research ethics review board. All participants provided written informed consent. Institutional review board approval was waived for this analysis because of the publicly available and deidentified data. The study protocol was authorized by National Center for Health Statistics (NCHS) Research Ethics Review Board (Protocol #2005–06, #2011–17, #2018–01).

CRediT authorship contribution statement

Zeyan Li: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation. **Maoyan Wu:** Validation, Formal analysis, Conceptualization. **Simin Kong:** Formal analysis, Data curation. **Bin Xiao:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2025.103000.

Data availability

The datasets generated during and/or analysed during the current study are available in the National Health and Nutrition Examination Survey, https://www.cdc.gov/nchs/nhanes/index.htm.

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