The Magnesium Depletion Score is associated with increased likelihood of kidney stone disease among female adults

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Abstract

Object: The association between magnesium depletion score (MDS) and kidney stone disease (KSD) remains unknown. This study was designed to investigate the association of MDS with KSD in adults.

Methods: A total of 19,654 participants were enrolled from the National Health and Nutrition Examination Surveys (NHANES). The MDS was calculated by assessing four aspects, including alcohol assumption, renal function, and use of diuretics and proton pump inhibitor (PPI). Multivariable logistic regressions were performed to explore the associations between MDS and the prevalence of KSD. Linear correlations were conducted explore the relationship of testosterone with MDS.

Results: In the multivariable logistic regressions with full adjustment for confounding variables, the odds ratio of MDS associating with KSD was 1.28 (95% CI: 1.04–1.58, *P* = 0.022) in total population, and 1.70 (95% CI: 1.16–2.50, *P* = 0.007) in female participants. Besides, compared to the lowest MDS, the highest MDS was associated with a lower testosterone (β = -11.548, *P* = 0.001) after full adjustment in non-menopause women.

Conclusion: This study highlighted a positive correlation of high MDS with KSD in female population, which may be associated low level of serum testosterone.

1. Introduction

Magnesium, the fourth most abundant mineral and the second most abundant intracellular divalent cation, is an essential macronutrient for the human body[1, 2]. Magnesium plays a role in more than 300 enzyme reactions in the human body, including muscle contraction, nerve transmission and cardiac excitability, regulating blood pressure and maintaining the immune system and insulin metabolism[1–3]. Magnesium ions are essential in maintaining the anatomical and functional integrity of various organelles, including mitochondria and ribosomes[4]. Magnesium activates a variety of enzymes, aids in energy production, and helps regulate levels of calcium, copper, zinc, potassium, vitamin D, and other important nutrients in the body. Additionally, this mineral helps in the formation of teeth and bones[5].

The status of magnesium in the human body is closely related to many diseases. Hypomagnesemia is clinically defined as a serum magnesium concentration < 0.75 mmol/L[6], with early nonspecific symptoms including loss of appetite, nausea, vomiting, fatigue, and lethargy. After significant magnesium deficiency occurs, patients often present with increased neuromuscular excitability, cardiac arrhythmias, pregnancy complications, osteoporosis, and impaired motor function[6]. In recent years, more and more studies have found that magnesium deficiency is associated with oxidative stress, cardiovascular disease, cognitive impairment and metabolic syndrome[7–12]. Some researches proposed that low extracellular Mg^{2+} slows down endothelial cell proliferation, stimulates monocyte adhesion, significantly damages endothelial function, affects vascular structure and function, and stimulates atherosclerosis formation[13, 14]. Moreover, there is a correlation between the amount of serum magnesium and the formation of kidney stone disease (KSD). Subjects with relatively low serum magnesium levels, even within the normal range, have a higher prevalence of kidney stones[15].

Kidney stones as the most common type of urolithiasis had an increasing prevalence over the past decades, placing high costs and clinical burdens on the healthcare system[16]. Many metallic elements are closely linked to the mechanisms of stone formation [17]. Approximately 80% of kidney stones are composed of calcium oxalate (CaOx) mixed with calcium phosphate (CaP), others composed of uric acid, struvite, and cystine are also common, accounting for approximately 9%, 10%, and 1% of stones respectively [18]. In the intestine and urine, magnesium and calcium compete for binding to oxalic acid. However, compared to calcium oxalate, which is more difficult to dissolve in water, magnesium oxalate is not as prone to stone formation at normal physiological concentrations in urine. Magnesium can also bind oxalates in the gastrointestinal tract and reduce their absorption. Through different mechanisms, a low magnesium state leads to poor urinary magnesium excretion and leads to urinary calcium oxalate supersaturation with an increased likelihood of formation of insoluble complexes [19]. It has recently been reported in the literature that women with polycystic ovary syndrome (PCOS), particularly those who present with irregular menstruation and polycystic ovary morphology (PCOM) on ultrasound, have a higher likelihood of developing kidney stones [20].

Magnesium homeostasis is maintained by the intestines, bones, and kidneys. After daily intake of magnesium, only about 24–76% is absorbed by the small intestine and stored in the bones, and excess magnesium is excreted by the kidneys and intestines[21]. Under physiological conditions, about 2400 mg of magnesium in plasma is filtered by the glomeruli of kidney[22]. Of the filtered load, 95% magnesium is immediately reabsorbed and only 3–5% is excreted in the urine[23]. Intestinal absorption is not directly proportional to magnesium intake, but mainly depends on magnesium status. When serum magnesium levels are lower, the intestine absorbs more of this element, so when intake is low, the relative absorption of magnesium is high[24]. Since most magnesium is stored in cells and bones, it is difficult to accurately assess magnesium status in the human body. Currently, serum magnesium testing is fast and convenient and remains the standard commonly used to assess human magnesium status in clinical and research settings. In order to evaluate the status of magnesium in the body from more dimensions, magnesium depletion score (MDS) is introduced for further study.

Fan et al. developed the MDS, a composite score aggregating 4 established risk factors, which also considers the pathophysiological factors influencing the kidneys' reabsorption capability [25]. The developed model of MDS, coupled with sex and age, may serve as a promising measure to identify magnesium deficiency and systemic inflammation and predict risk of CVD mortality and chronic disease.

However, to our knowledge, the association between the MDS and stone formation has not been studied. This study aimed to investigate whether MDS is an independent determinant for the presence of KSD by examining data from a nationally representative sample of adults.

2. Materials and Methods

2.1 Data source and survey design for the NHANES

The National Health and Nutrition Examination Survey (NHANES) driven by National Center for Health Statistics (NCHS) is a program of studies designed to assess the health and nutritional status of adults and children in the United States. This program produces vital and health statistics publicly through questionnaires and physical examination.

This cross-sectional analysis obtained data from the 2007–2020 NHANES cycles. A total of 19,654 adults over 18 years old were included for analysis, who have medical records of KSD, without self-reported pregnancy, lactation, or current illegal drug use (Fig. 1). Written informed consent to participate was obtained from each participant. This research followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline [26].

The outcome is KSD. We defined KSD by combining self-reported physician diagnoses and standardized medical status questionnaires completed during personal interviews. Participants were asked: “Have you ever had kidney stones?”. We excluded those who refused to answer and those who answered “don’t know”.

2.2 MDS calculation and dietary intakes of magnesium, calcium and vitamin D

The calculation [27] [28]of MDS includes four aspects, 1) alcohol drinking (heavy drinker for 1 point, heavy drinkers are defined as > 1 drink/day for women and > 2 drinks/day for men), 2) diuretic use (current use for 1 point), 3) proton pump inhibitor (PPI) use (current use for 1 point), 4) kidney function [60 mL / (min · 1.73 m2) ≤ estimated glomerular filtration rate (eGFR) < 90 mL/ (min · 1.73 m2) for 1 point; eGFR < 60 mL/ (min · 1.73 m2) for 2points. MDS calculates the total score of these four items, and the scores is integer ranging from 0–5. Among them, MDS scored 3, 4, and 5 are combined into one group due to too few people, and the grouping of MDS is MDS1 (score = 0, n = 5699), MDS2 (score = 1, n = 7821), MDS3 (score = 2, n = 4204), and MDS4 (score = 3–5, n = 1930).

Dietary supplement is closely associated with the occurrence of kidney stones [29]. Thus, daily intake estimation is of the essence. NHANES conducted two 24-hour dietary recalls using the Automated Multichannel Method (AMPM), collected 10 days apart, and participants also provided details on supplement use over a 30-day period. For the daily intake estimation, the daily supplement dosage is calculated by combining the product information on the ingredients, the amount and unit per serving. Total intake of nutrients, such as vitamin D, magnesium, and calcium, was estimated based on the average intake of two 24-hour dietary recalls and supplement intake over a 30-day period.

2.3 Assessment of covariates

Several important covariates were selected to assess the effects of confounding factors. Continuing variables included age, body mass index (BMI), serum total cholesterol (TC), serum triglycerides (TG), serum uric acid (sUA), serum calcium (sCa), serum phosphorus (sP), magnesium intake, calcium intake, vitamin D intake. Gender and occupation were the categorical variable. Missing values are processed as deletions.

2.4 Statistical analysis

All analyses followed the NHANES protocol of statistical analyses and accounted for NHANES sampling weights. The continuous variables are presented with survey-weighted mean (95% Cl), while the p-value was calculated by survey-weighted linear regression (svyglm). For the categorical variables, survey-weighted percentage (95% Cl) and p- value obtained by survey-weighted Chi-square test (svytable) are showed. Since the serum klotho data deviated significantly from a normal distribution, Klotho concentrations were ln transformed in logistic regression. The association of MDS with KSD, and odds ratios (ORs) and 95% confidence intervals (Cls) were assessed by investigating weighted multivariable logistic regressions after adjusting for potential confounders, whereas the adjusted model 2 included the crude model plus demographic characteristics like age, gender, and BMI, and model 3 is based on model 2 and adds clinical features, such as sCa, sP, TC, TG, sUA and so on. Subgroup analysis stratified by sex, intakes of magnesium, and age. Finally, we used interaction tests to evaluate differences in the effect of MDS on KSD between different subgroups. Linear correlations were conducted explore the relationship of testosterone with MDS. All statistical analyses were conducted with survey packages in R version 4.2.1, and $P < 0.05$ stands for statistical significance.

3. Results

3.1 Baseline characteristics of study participants

This study embraced 19,654 participants with the age of approximately 53.48 years and with 8725 males (44.39%, not weighted). The weighted distribution of demographic and clinical characteristics from these participants was shown in Table 1.

Table 1
Basic characteristics of participants, weighted

Characteristics		Magnesium Depletion Score					
	Overall	0	1	2	3	4	5
	n = 19654	n = 5699	n = 7821	n = 4204	n = 1587	n = 326	n = 17
Age (years)	53.48(52.98, 53.98)	48.78(48.23, 49.33)	51.17(50.51, 51.83)	60.70(59.91, 61.49)	67.13(66.25, 68.00)	70.35(68.81, 71.88)	67.49(63
20–39	30.55(30.21, 30.89)	31.08(30.62, 31.53)	29.81(29.41, 30.21)	32.23(31.51, 32.95)	33.78(32.16, 35.40)	39#	/
40–59	50.25(50.03, 50.46)	49.84(49.50, 50.17)	50.06(49.75, 50.37)	50.95(50.41, 51.49)	52.91(52.14, 53.68)	51.22(48.67, 53.77)	43.53(39
60 and over	70.15(69.92, 70.37)	67.57(67.25, 67.90)	69.55(69.19, 69.90)	71.34(70.87, 71.82)	72.88(72.32, 73.45)	73.76(72.56, 74.96)	69.98(67
Gender (%)							
Male	42.80(42.00, 44.00)	40.60(38.70, 42.00)	42.80(41.20, 44.00)	46.00(43.90, 48.00)	45.10(41.60, 49.00)	41.90(34.50, 50.00)	41.79(2.1 *
Female	57.20(56.30, 58.00)	59.40(57.60, 61.00)	57.20(55.60, 59.00)	54.00(52.00, 56.00)	54.90(51.30, 58.00)	58.10(50.40, 65.00)	58.21(3.0 100) *
BMI (Kg/m^2)	29.71(29.53, 29.89)	29.36(29.08, 29.65)	29.38(29.15, 29.61)	30.26(30.20, 30.73)	30.90(30.38, 31.42)	32.24(31.16, 33.30)	37.18(31
Laboratory test							
eGFR (min*1.73m^2)	95.05(94.41, 95.69)	108.55(108.07, 109.03)	99.01(98.26, 99.77)	78.43(77.34, 79.52)	61.13(59.77, 62.49)	48.93(46.17, 51.69)	46.11(41
TC (mmol/L)	5.01(4.98, 5.04)	5.07(5.02, 5.12)	5.01(4.97, 5.06)	4.99(4.95, 5.04)	4.85(4.76, 4.94)	4.61(4.41, 4.80)	4.72(4.16
TG (mmol/L)	1.81(1.78, 1.85)	1.81(1.74, 1.88)	1.76(1.72, 1.80)	1.87(1.82, 1.92)	1.99(1.90, 2.08)	1.87(1.74, 2.00)	1.94(1.62
sCa (mmol/L)	2.35(2.35, 2.35)	2.34(2.34, 2.35)	2.35(2.35, 2.36)	2.36(2.35, 2.36)	2.36(2.35, 2.37)	2.34(2.32, .36)	2.32(2.26
sP (mmol/L)	1.21(1.21, 1.22)	1.21(1.20, 1.22)	1.21(1.20, 1.21)	1.21(1.20, 1.22)	1.23(1.21, 1.25)	1.24(1.20, 1.27)	1.27(1.21
sUA (μmol/L)	324.26(322.22, 326.29)	301.39(298.57, 304.20)	316.20(313.57, 318.83)	351.74(348.02, 355.45)	388.98(381.92, 396.04)	423.81(407.94, 439.68)	416.14(3
Dietary intake							
Mg (mg/d)	301.94(295.19, 308.68)	304.69(293.08, 316.31)	304.97(298.15,311.79)	298.94(289.46, 308.42)	284.08(272.47, 295.69)	263.74(241.47, 286.00)	260.06(2 301.12)
Ca (mg/d)	1042.73(1022.73, 1062.73)	1040.81(1011.56, 1070.06)	1057.56(1033.99,1081.13)	1034.78(999.39, 1070.18)	989.62(942.53, 1036.71)	959.11(847.54, 1070.68)	1272.09(1569.69)
VD (μg/d)	18.76(17.58, 19.95)	19.01(16.62, 21.40)	16.95(15.42,18.49)	20.78(18.12, 23.44)	23.26(19.47, 27.05)	20.82(13.71, 27.92)	19.74(4.3
SKL (pg/ml)	838.69(827.97, 849.41)	876.51(860.98, 892.05)	844.81(830.64, 858.97)	807.84(791.65, 824.04)	758.54(728.31, 788.77)	692.05(653.04, 731.06)	634.94(4 774.29)

Only 2 participants in this subgroup, and they are both 39 years old

* Only 17 participants in the subgroup (MDS score = 5), of which eight of whom are male and nine of whom are female

For continuous variables: survey-weighted mean (95% CI), the *p*-value was calculated by survey-weighted linear regression (svyglm). For categorical variables: survey-weighted percentage (95% CI), the *p*-value was calculated by survey-weighted Chi-square test (svychisq).

There were significant differences in the distribution of these indicators among MDS groups, except for serum phosphorus (sP) and daily intake of Calcium (Ca) and vitamin D (VD). It was worth noting that most indicators increased with the increase of MDS, especially serum klotho (SKL) (Table 1). As MDS increased, the prevalence of kidney stones also increased, showing a gentle increase in men, while in women, the prevalence increases sharply in the high MDS group (Fig. 2).

3.2 Association of MDS with prevalence of KSD

The weighted multivariate logistic regression was conducted to evaluate the association of MDS with KSD, as shown in Table 2. In the unadjusted model 1, MDS4 was positively correlated with the risk of KSD (OR = 1.60, 95% CI: 1.32–1.94, $P < 0.001$). After adjustment for relative confounders, this positive association was still significant after minimal adjustment (OR = 1.24, 95% CI: 1.01–1.51, $P = 0.037$) and full adjustment (OR = 1.28, 95% CI: 1.04–1.58, $P = 0.022$). According to intake recommendations for magnesium provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences) [30] [31], daily magnesium intake level was divided into two groups (IM1 < 420 mg/d and IM2 > = 420 mg/d). However, the level of magnesium intake was not associated with the prevalence of kidney stones in three logistic regression model.

Table 2
Associations of MDS and intake of Mg with kidney stone

	Model 1			Model 2			Model 3		
	estimated β	OR (95% CI)	*P* value	estimated β	OR (95% CI)	*P* value	estimated β	OR (95% CI)	*P* value
MDS group:									
1	reference			reference			reference		
2	0.07	1.07(0.90, 1.27)	0.449	0.03	1.03(0.87, 1.22)	0.742	0.04	1.05(0.88, 1.24)	0.601
3	0.27	1.31(1.10, 1.60)	**0.003**	0.08	1.09(0.91, 1.31)	0.360	0.11	1.11(0.93, 1.34)	0.239
4	0.47	1.60(1.32, 1.94)	**< 0.001**	0.21	1.24(1.01, 1.51)	**0.037**	0.25	1.28(1.04, 1.58)	**0.022**
Intake of Mg:									
IM1	reference			reference			reference		
IM2	-0.07	0.92(0.78, 1.09)	0.355	-0.15	0.86(0.72, 1.03)	0.092	-0.15	0.86(0.71, 1.04)	0.111
Model 1 unadjusted									

Model 2 adjusted for age, gender and BMI

Model 3 further adjusted sCa, sP, TC, TG, sUA, intake of Mg, intake of Ca and intake of VD

3.3 Higher MDS in female population is associated with a higher prevalence of KSD

We explored the possible relationships of MDS with KSD in gender subgroups (Table 3). The female population revealed a significant association between MDS and KSD. In model 1, no covariates were adjusted, positive associations were observed between MDS3 and KSD (OR = 1.32, 95% CI: 1.01–1.73, $P = 0.041$), and MDS4 and KSD (OR = 1.77, 95% CI: 1.21–2.58, $P = 0.003$). Model 2 were adjusted for age and BMI, the positive association was still significant with MDS4 and KSD (OR = 1.66, 95% CI: 1.13–2.43, $P = 0.009$). Model 3 was full adjusted with adding sCa, sP, TC, TG, sUA, intake of Mg, intake of Ca and intake of VD, MDS4 was still positively related to KSD (OR = 1.70, 95% CI: 1.16–2.50, $P = 0.007$). However, contrary to what we expected, this positive correlation was not observed after adjusting the logistic regression model in the male population.

Table 3
Associations of MDS with kidney stone in gender groups

	Model 1			Model 2			Model 3		
	estimated β	OR (95% CI)	*P* value	estimated β	OR (95% CI)	*P* value	estimated β	OR (95% CI)	*P* value
MDS group in male participants:									
1	reference			reference			reference		
2	0.06	1.07(0.87, 1.31)	0.530	-0.03	1.03(0.87, 1.22)	0.754	-0.03	0.97(0.79, 1.20)	0.794
3	0.22	1.25(1.01, 1.54)	**0.040**	-0.08	1.09(0.91, 1.31)	0.439	-0.08	0.93(0.73, 1.18)	0.526
4	0.33	1.39(1.07, 1.83)	**0.014**	-0.11	1.24(1.01, 1.51)	0.521	-0.09	0.92(0.66, 1.27)	0.591
MDS group in female participants:									
1	reference			reference			reference		
2	0.05	1.05(0.81, 1.37)	0.712	0.05	1.05(0.81, 1.35)	0.708	0.06	1.05(0.88, 1.24)	0.630
3	0.28	1.32(1.01, 1.73)	**0.041**	0.23	1.26(0.95, 1.69)	0.109	0.25	1.06(0.82, 1.38)	0.091
4	0.57	1.77(1.21, 2.58)	**0.003**	0.51	1.66(1.13, 2.43)	**0.009**	0.53	1.70(1.16, 2.50)	**0.007**

Model 1 unadjusted

Model 2 adjusted for age and BMI

Model 3 further adjusted sCa, sP, TC, TG, sUA, intake of Mg, intake of Ca and intake of VD

3.4 Higher MDS in non- menopaused female population is associated with a lower level of serum testosterone

The study selected the participants with testosterone (TST) data from NHANES 2011–2016 cycle for in-depth analysis. After adjustment for relative confounders, this positive association was still significant in model 2 with testosterone (OR = 1.98, 95% CI: 1.17–3.34, *P* = 0.012) and full adjustment (OR = 2.06, 95% CI: 1.24–3.43, *P* = 0.006) (Table 4). Further, interaction tests were conducted to evaluate differences in the effect of TST on MDS between different subgroups and no interactions were observed (supplementary). To explore the correlation between TST and MDS, we further divided the female participants into two groups according to whether they were menopausal or not. According to the American College of obstetricians and gynecologists, the average age that American women go through menopause is 51 years. In non-menopausal women (< 51 years old), MDS4 was significantly negatively correlated with TST (*P* = 0.001), whereas in menopausal women (≥ 51 years old), this correlation disappeared after adjusting for occupation (Table 5).

Table 4
Associations of MDS with kidney stone adjusting for TST in gender groups from 2011–2016

	Model 1			Model 2			Model 3		
	estimated β	OR (95% CI)	*P* value	estimated β	OR (95% CI)	*P* value	estimated β	OR (95% CI)	*P* value
MDS group in male participants:									
1	reference			reference			reference		
2	-0.03	0.97((0.71, 1.32)	0.844	-0.14	0.87(0.62, 1.23)	0.431	-0.12	0.89(0.64, 1.23)	0.470
3	0.11	1.12(0.82, 1.53)	0.468	-0.25	0.78(0.56, 1.09)	0.145	-0.21	0.81(0.57, 1.15)	0.229
4	0.34	1.40(0.96, 2.03)	0.078	-0.17	0.84(0.53, 1.34)	0.458	-0.08	0.92(0.58, 1.48)	0.738
MDS group in female participants:									
1	reference			reference			reference		
2	0.11	1.12(0.78, 1.60)	0.548	0.12	1.13(0.80,1.59)	0.472	0.14	1.15(0.81,1.62)	0.418
3	0.26	1.30(0.86, 1.95)	0.205	0.27	1.31(0.84,2.05)	0.221	0.29	1.34(0.86,2.08)	0.192
4	0.65	1.92(1.11, 3.32)	**0.021**	0.68	1.98(1.17,3.34)	**0.012**	0.72	2.06(1.24,3.43)	**0.006**
Model 1 unadjusted									

Model 2 adjusted for age, BMI and testosterone

Model 3 further adjusted sCa, sP, TC, TG, sUA, intake of Mg, intake of Ca and intake of VD

Table 5
Linear regression analysis for the association of TST and MDS in female participants

	Non-menopause				Menopause			
	Model 1		Model 2		Model 1		Model 2	
	Mean difference	*P* value	Mean difference	*P* value	Mean difference	*P* value	Mean difference	*P* value
MDS1	reference		reference		reference		reference	
MDS2	0.703	0.705	-0.632	0.810	2.980	**0.030**	4.397	0.067
MDS3	-2.779	0.302	-4.088	0.285	0.284	0.745	3.764	0.072
MDS4	-9.090	**0.002**	-11.548	**0.001**	0.944	0.608	5.442	0.521
Model 1 unadjusted								
Model 2 adjusted for occupation								

4. Discussion

This study provided a comprehensive analysis of MDS and KSD, and after controlling for potential covariates, a positive correlation between higher MDS and KSD in adults was observed in the 2007–2020 NHANES, and this significant positive correlation was also found in a subgroup of women in 2011–2016. TST was significantly negatively associated with MDS in this female subgroup.

Magnesium depletion is positive associated with KSD. To our knowledge, ours is the first study to examine the association between the kidney reabsorption-related magnesium depletion status and KSD. As we mentioned before, MDS was evaluated from for aspects, including alcohol, renal function, PPI and diuretics use. Maintaining magnesium balance in the body is heavily dependent on the normal functioning of the kidneys. Researchers have long explored the correlation between kidney stones and renal function. Vupputuri et al. [32] were the first to study the correlation between kidney stones and chronic kidney disease (CKD). They found that the number of patients with CKD who had a history of kidney stones was nearly twice that of the control group. The causal relationship between the two is uncertain. Repeated stone obstruction can lead to kidney damage, and problems such as renal function excretion after kidney damage may aggravate kidney stones. PPI use was associated with a dose-dependent increase in risk of kidney stones in a large cohort study [33]. PPI-induced hypomagnesemia is caused by intestinal malabsorption of Mg^{2+} [34, 35] and results in decreased urinary magnesium, a well-known inhibitor of stone formation. However, most diuretic therapy may result in excessive urinary loss of magnesium [36], inconsistent with the impression that high urinary magnesium reduces stone formation. In the study of the relationship between serum magnesium and kidney stones, we found that some studies suggested that there is a negative correlation between serum magnesium and kidney stones [15] [37]. The reason may be that magnesium can reduce stone formation by directly inhibiting the nucleation and growth rate of calcium oxalate crystals. Second, magnesium may reduce intestinal absorption of oxalates. On top of this, the application of some diuretics will also lead to increased urinary calcium excretion [36] and increased calcium oxalate formation. Further research by grouping patients according to the types of diuretics they use can uncover deeper mechanisms. As early as a few years ago, researchers proposed that alcoholism and large amounts of alcohol intake would reduce the body's magnesium content. The reason may be related to ethanol's reduction in the activity of calcium-dependent potassium channels [38]. A large prospective cohort [39] found that people who drank more alcohol had a reduced risk of kidney stones, which may simply be related to increased fluid intake. Although alcohol has a strong magnesium diuretic effect, it can also cause an increase in the amount and rate of excretion of other electrolytes [40]. As long-term drinking progresses, the body's magnesium stores become depleted and urinary excretion of magnesium may decrease, which is why long-term drinking may increase the prevalence of stones.

To our surprise, in the female population, high MDS was significantly correlated with KSD, whereas in the male population this correlation disappeared. In conventional perception, men are more likely to suffer from kidney stones than women [41], and kidney formation are negatively correlated with serum testosterone levels [42]. That is why we further analyzed the relationship of MDS with TST and found a significant negative correlation between them. Some literature suggests that magnesium supplementation can elevate serum testosterone levels in male participants [43] [44], even older man [45]. This may indicate that high serum magnesium status may be associated with high serum TST. Chandra et al. showed significant enhancing in steroidogenic enzymes, namely, delta(5)3beta-hydroxysteroid dehydrogenase and 17beta-hydroxysteroid dehydrogenase, activities at moderate and high dose of magnesium that resulted in increased serum TST levels. In recent years, evidence of magnesium-mediated changes in TST - sex hormone binding globulin (SHBG) affinity has been found by high performance liquid chromatography (HPLC). Magnesium binds to SHBG in a non-specific manner, leading to non-competitive inhibition of TST - binding to SHBG, thereby increasing the availability of biological TST, and magnesium binding to SHBG is accompanied by magnesium release [46]. Huang et al. raised that serum TST may be a protective factor in men over 40 years too [42]. However, recent researches have suggested that female patients with PCOS are two to three times more likely to develop kidney stones[20] and that low serum magnesium status in these patients may be associated with higher testosterone levels [47]. It appears that these results are inconsistent with ours, but it is worth note that patients with PCOS, which is characterized by chronic low-level inflammation [48], are prone to suffer from kidney stone formation resulting from immune dysregulation. However, current issues regarding magnesium metabolism and testosterone remain controversial, and it is hoped that detailed basic experiments in the future can provide new perspectives.

Our study has several limitations that should be taken into consideration. Firstly, due to the cross-sectional study design, we cannot establish a causal relationship between MDS and KSD. Secondly, it is important to note that all participants in this study were located in the United States and therefore may not be representative of the entire global population. Lastly, it is worth mentioning that the lack of serum magnesium and urinary magnesium data in the NHANSE database makes it impossible to determine the relationship between magnesium excretion and intake.

5. Conclusion

In summary, we demonstrated that there is a positive correlation of high MDS with KSD in female population, which may be associated with low level of serum TST. Longitudinal studies and clinical trials are required to assess the causal relationship of magnesium homeostasis and kidney stone formation in the future.

Declarations

Statements & Declarations

Funding

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Competing Interests

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

Author Contributions

All authors contributed to the study conception and design. Conceptualization of this work were proposed by [Zhiyong Guo], [Wei Chen] and [Hui Shen]. Material preparation, data collection and analysis were performed by [Ying Xu], [Yingyi Qin] and [Hongtao Lu]. Validation and formal analysis were conducted by [Lulu Liu], [Weiyan Huang], [Anwen Huang] and [Yufei Ye]. The first draft of the manuscript was written by [Ying Xu], [Wei Chen] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets analyzed during the current study are available in the National Health and Nutrition Examination Survey [https://www.cdc.gov/nchs/nhanes/index.htm].

Ethics approval

This is an observational study. The NCHS Research Ethics Committee has confirmed that no ethical approval is required.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Figures

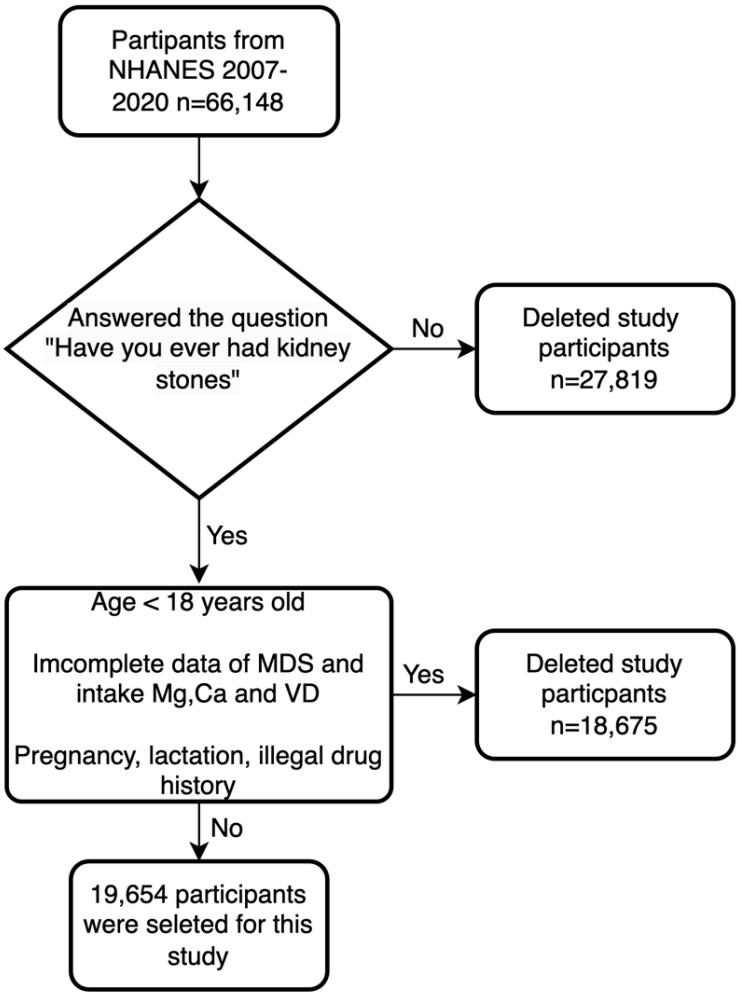

Figure 1

Procedures for screening participants

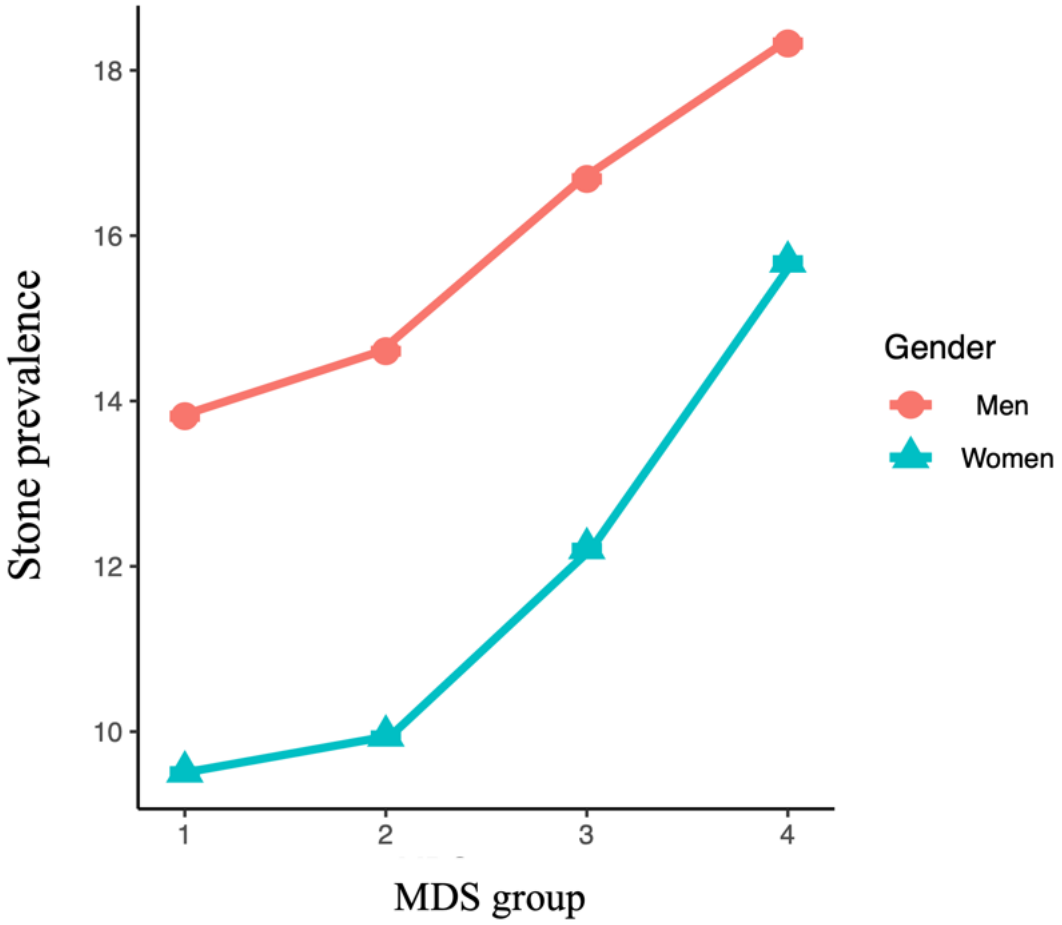

Figure 2

Line chart of changes in kidney stone prevalence over MDS groups

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