Original Article

Association of chronic constipation and chronic diarrhea with renal stones: a cross-sectional study of the National Health and Nutrition Examination Survey 2007–2010

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Background: Renal stone is a highly prevalent life-long disease with a high recurrence rate. Chronic bowel diseases, including chronic gastrointestinal symptoms (chronic constipation or chronic diarrhea), are common gastrointestinal problems. We aimed to evaluate the associations of chronic constipation and chronic diarrhea with renal stones.

Methods: This large-scale, cross-sectional study was performed within participants (≥20 years old) from the National Health and Nutrition Examination Survey from 2007 to 2010. Logistic regression and sensitivity analyses were conducted to clarify the association between chronic bowel diseases and renal stones.

Results: A total of 8,067 participants aged ≥20 years were included. The prevalence of renal stones is 9.14%. Chronic diarrhea was positively related to the risk of renal stones [odds ratio (OR) =1.681, 95% confidence interval (CI): 1.212 to 2.330, P=0.004] after adjusting for all covariates. In participants with body mass index (BMI) over 30 kg/m^2, chronic constipation was correlated with kidney stones in fully adjusted model 2 (OR =2.142, 95% CI: 1.389 to 3.303, P=0.004).

Conclusions: Our findings provide evidence that chronic diarrhea is associated with an increased risk of renal stones. Chronic constipation is positively related to the risk of renal stones in participants with BMI over 30 kg/m^2. Health care should focus more on bowel health status for the prevention of related diseases. More prospective cohort studies are needed.

Keywords: Chronic bowel disease; renal stone; constipation; diarrhea; National Health and Nutrition Examination Survey (NHANES)

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Introduction

Renal stone is a highly prevalent urological disease worldwide (1), with a high recurrence rate of approximately 50% within five years (2). Currently, kidney stone disease expends $2 billion each year, causing great health and economic burdens to patients (3). The development of renal stone is a complex process affected by multiple risk factors, such as genetic factors, anatomical abnormalities, imbalanced dietary habits, metabolic diseases, and others (4).

Previous studies show that host components (e.g., host immune system) affect the microbial community (5,6). Pathogenetic changes in microorganisms contribute to noncommunicable diseases, including inflammatory bowel disease (IBD), metabolic diseases, and others (6). Chronic bowel diseases are the most common gastrointestinal problems, including chronic gastrointestinal symptoms (i.e., chronic constipation and chronic diarrhea). Chronic constipation and chronic diarrhea are two common bowel habit abnormalities. However, the association of chronic constipation and chronic diarrhea with renal stones is still under-studied and needs to be clarified.

Hence, we performed the current study using the National Health and Nutrition Examination Survey (NHANES) dataset to identify the relationships of chronic constipation and chronic diarrhea with the risk of kidney stones. We hypothesized that chronic bowel diseases were related to high risk of kidney stones. We present this article in accordance with the STROBE reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-212/rc).

Methods

Study population

NHANES is a prospective cross-sectional study with interviews and examinations every two years. We enrolled 20,686 participants aged 20 years and above from 2007 to 2010. Then participants with missing information on renal stones and chronic bowel diseases were excluded. Finally, 8,067 participants were eligible for complete case analysis. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The ethical review board of the National Center for Health Statistics granted approval to the NHANES protocols. Written informed consent was acquired by the NHANES for participating in the survey.

Assessment of chronic constipation and chronic diarrhea

Based on previous studies (7,8), participants who were considered to have chronic constipation or chronic diarrhea were enrolled according to the Bowel Health Questionnaire section. The questionnaire was performed in the NHANES Mobile Examination Center (MEC) by well-trained interviewers. The Bristol Stool Form Scale (BSFS) was used to evaluate bowel health status (9). Chronic constipation was defined as a usual or most common stool type of BSFS Type 1 (separate hard lumps, like nuts) or Type 2 (sausage-like, but lumpy). Chronic diarrhea was determined by a usual or most common stool type of BSFS Type 6 (fluffy pieces with ragged edges, a mushy stool) or Type 7 (watery, no solid pieces). The other subjects were identified as having normal or asymptomatic bowel health status.

Renal stone assessment

A history of renal stone was determined by the questionnaire "Have you ever had kidney stones?" (10). A "yes" response indicates a renal stone history before.

Covariates

Based on previous studies (11,12), we included demographic data (i.e., age, education level which is divided by high school degree, family income-to-poverty ratio which is divided by 1.3 and 3.5, and race, physical examination [e.g., body mass index (BMI), kg/m^2], and questionnaires [e.g., recreational activities (none, moderate activity, vigorous activity), smoking history and alcohol consumption history (<1 time per week, 1–3 times per week, or ≥4 times per week)]. The BMI was classified as ≤20, >20 ≤25, >25 ≤30, or >30 kg/m^2 groups. Diabetes mellitus (DM) was diagnosed according to a previous study (13).

Statistical analysis

The sampling weights, strata, and primary sample units were used according to the Centers for Disease Control and

Highlight box

Key findings
- Chronic diarrhea correlates with high risk of kidney stones.
- Chronic constipation is positively associated with the risk of kidney stones in participants with body mass index (BMI) over 30 kg/m^2.

What is known and what is new?
- Kidney stone disease is highly prevalent with a high recurrence rate. However, the etiologies and mechanism of stone formation is largely unknown.
- This study identified potential associations of chronic constipation and chronic diarrhea with kidney stones.

What is the implication, and what should change now?
- Emerging evidence indicates the impact of chronic bowel diseases on the formation of kidney stones, which is expected to arouse great attention in the future.
- Health care should focus more on bowel health status for the prevention of related diseases.

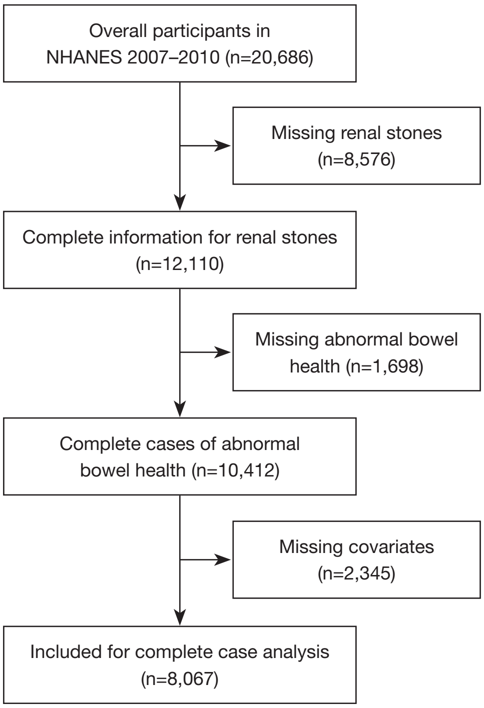

Figure 1 Participant screening of NHANES 2007–2010. NHANES, National Health and Nutrition Examination Survey.

Prevention (CDC) guidelines, which is publicly available at https://wwwn.cdc.gov/nchs/nhanes/tutorials/default.aspx. Continuous variables were presented by mean ± standard deviation (SD), while the categorical variables were presented as counting numbers (n). Survey-weighted linear regression was applied for analysis of continuous variables, while a survey-weighted chi-square test was used for analysis of categorical variables. To clarify the correlation between chronic bowel diseases and renal stones, three logistic regression models were conducted. No covariates were adjusted in crude model. The fully-adjusted model was adjusted for all covariates. To examine the sensitivity of the outcome, we performed multiple imputation by using the *R* multiple imputation procedure to process missing data on independent variables (14,15).

The sampling weight was chosen according to the guidelines of the NHANES database (https://www.cdc.gov/nchs/nhanes/index.htm). *R* software version 4.1 (http://www.R-project.org; The R Foundation) and EmpowerStats (http://www.empowerstats.com, X&Y Solutions, Inc., Xianyang, China) were used for the statistical analyses. A two-tailed P<0.05 indicated a significant difference.

Results

A total of 8,067 participants aged 20 years or older were included (*Figure 1*). The mean (SD) age was 49.31±17.33 years, with 46.45% males and 53.55% females. Most of the participants were non-Hispanic White (51.73%), above high school grade (73.51%), had a family income-to-poverty ratio between 1.3 and 3.5 (37.60%), were obese (37.30%), were previous smokers (52.60%), non-drinkers (62.37%), had little recreational activity (53.01%), without DM (82.47%), hypertension (58.42%) and coronary heart disease (95.74%). The renal stones prevalence rate was 9.14% in the whole US population. In participants with chronic constipation, the incidence of renal stone was 9.03%. The prevalence of renal stone in the chronic diarrhea group was 13.72% (*Table 1*).

In the crude model l, there was a significant difference in the outcome between patients with chronic diarrhea and those with renal stones [odds ratio (OR) =1.785, 95% confidence interval (CI): 1.365 to 2.334, P<0.001] (*Table 2*). Model 1 revealed that chronic diarrhea was still a risk factor for renal stones (OR =1.741, 95% CI: 1.305 to 2.322, P=0.001). A fully adjusted model 2 revealed similar results (OR =1.681, 95% CI: 1.212 to 2.330, P=0.004). Subgroup analysis revealed no effect modifiers for the association of chronic constipation or chronic diarrhea with renal stones (Table S1). Furthermore, we investigated whether diarrhea or constipation is a risk factor for kidney stones in people stratified by BMI (*Table 3*). In participants with BMI over 30 kg/m^2, chronic constipation was positively correlated with the risk of kidney stones after adjustment for all covariates (OR =2.142, 95% CI: 1.389 to 3.303, P=0.004). A similar relationship was also found in participants with chronic diarrhea in the 25–30 kg/m^2 BMI subgroup (OR =2.509, 95% CI: 1.460 to 4.312, P=0.002) compared with none chronic bowel disease group.

Furthermore, we performed a sensitivity analysis using multiple imputation method. A comparison between the complete case analysis and multiple imputation analysis was performed. The distribution of the data was similar, and the incidence rates in the complete case analysis and multiple imputation analysis were 9.14% and 9.21% respectively (Table S2). The fully adjusted model in multiple imputation analysis showed a significant difference between chronic diarrhea and renal stones (OR =1.527, 95% CI: 1.128 to 2.068, P=0.006) (*Table 4*).

Table 1 Basic characteristics of the study population in NHANES 2007–2010 (n=8,067)

Characteristics	All	Chronic bowel disease			P value
		None (N=6,813)	Chronic constipation (N=576)	Chronic diarrhea (N=678)	
Age (years)	49.31±17.33	49.11±17.35	47.20±17.84	53.11±16.14	<0.001
Gender					<0.001
Male	3,747 (46.45)	3,025 (44.40)	364 (63.19)	358 (52.80)	
Female	4,320 (53.55)	3,788 (55.60)	212 (36.81)	320 (47.20)	
Race					0.007
Non-Hispanic Black	1,511 (18.73)	1,253 (18.39)	129 (22.40)	129 (19.03)	
Non-Hispanic White	4,173 (51.73)	3,590 (52.69)	262 (45.49)	321 (47.35)	
Hispanic/Mexican	2,088 (25.88)	1,719 (25.23)	164 (28.47)	205 (30.24)	
Other race	295 (3.66)	251 (3.68)	21 (3.65)	23 (3.39)	
Education level					<0.001
≤ High school	2,137 (26.49)	1,688 (24.78)	182 (31.60)	267 (39.38)	
> High school	5,930 (73.51)	5,125 (75.22)	394 (68.40)	411 (60.62)	
Family income-to-poverty ratio					<0.001
<1.3	2,411 (29.89)	1,948 (28.59)	206 (35.76)	257 (37.91)	
≥1.3, <3.5	3,033 (37.60)	2,570 (37.72)	218 (37.85)	245 (36.14)	
≥3.5	2,623 (32.52)	2,295 (33.69)	152 (26.39)	176 (25.96)	
BMI (kg/m^2)					0.006
≤20	337 (4.18)	275 (4.04)	32 (5.56)	30 (4.42)	
>20, ≤25	1,955 (24.23)	1,651 (24.23)	175 (30.38)	129 (19.03)	
>25, ≤30	2,766 (34.29)	2,355 (34.57)	191 (33.16)	220 (32.45)	
>30	3,009 (37.30)	2,532 (37.16)	178 (30.90)	299 (44.10)	
Smoking history					<0.001
Non-smoker	3,824 (47.40)	3,247 (47.66)	296 (51.39)	281 (41.45)	
Smoker	4,243 (52.60)	3,566 (52.34)	280 (48.61)	397 (58.55)	
Alcohol drinking history (drinks/week)					<0.001
<1	5,031 (62.37)	4,163 (61.10)	415 (72.05)	453 (66.81)	
1–3	2,082 (25.81)	1,823 (26.76)	119 (20.66)	140 (20.65)	
≥4	954 (11.83)	827 (12.14)	42 (7.29)	85 (12.54)	
Recreational activity					<0.001
None	4,276 (53.01)	3,506 (51.46)	348 (60.42)	422 (62.24)	
Moderate	2,125 (26.34)	1,837 (26.96)	124 (21.53)	164 (24.19)	
Vigorous	1,666 (20.65)	1,470 (21.58)	104 (18.06)	92 (13.57)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	All	Chronic bowel disease			P value
		None (N=6,813)	Chronic constipation (N=576)	Chronic diarrhea (N=678)	
Diabetes mellitus					<0.001
No	6,653 (82.47)	5,653 (82.97)	484 (84.03)	516 (76.11)	
Yes	1,414 (17.53)	1,160 (17.03)	92 (15.97)	162 (23.89)	
Hypertension					0.01
No	4,713 (58.42)	4,009 (58.84)	361 (62.67)	343 (50.59)	
Yes	3,354 (41.58)	2,804 (41.16)	215 (37.33)	335 (49.41)	
Coronary heart disease					0.048
No	7,723 (95.74)	6,528 (95.82)	553 (96.01)	642 (94.69)	
Yes	344 (4.26)	285 (4.18)	23 (3.99)	36 (5.31)	
Renal stone					<0.001
No	7,330 (90.86)	6,221 (91.31)	524 (90.97)	585 (86.28)	
Yes	737 (9.14)	592 (8.69)	52 (9.03)	93 (13.72)	

Data are presented as n (%) or mean ± standard deviation. NHANES, National Health and Nutrition Examination Survey; BMI, body mass index.

Table 2 Adjusted association of chronic bowel diseases with renal stones

Chronic bowel disease	Crude model†		Model 1‡		Model 2§	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
None	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–
Chronic constipation	1.059 (0.755, 1.483)	0.74	1.251 (0.895, 1.750)	0.20	1.263 (0.891, 1.790)	0.17
Chronic diarrhea	1.785 (1.365, 2.334)	<0.001	1.741 (1.305, 2.322)	0.001	1.681 (1.212, 2.330)	0.004

†, adjusted for none; ‡, adjusted for demographic characteristics (age, gender, race, family income-to-poverty ratio, and education level); §, adjusted for demographic characteristics in Model 1 and body mass index, smoking history, alcohol drinking history, recreational activity, diabetes mellitus, blood hypertension, and coronary heart disease. OR, odds ratio; CI, confidence interval.

Discussion

Based on a large-scale prospective cross-sectional sample of the NHANES dataset, the prevalence rate of renal stones was approximately 9.14% in the US population. Among the participants, 13.72% participants with chronic diarrhea had a history of renal stones. A total of 9.03% participants with renal stones reported chronic constipation. Our results revealed a positive association between chronic diarrhea and the risk of renal stones. However, the impact of chronic constipation on renal stones was not significant.

In our study, chronic diarrhea was associated with an increased risk of renal stones. Chronic diarrhea contributes to urolithiasis through multiple processes. Urolithiasis is a common health problem in the tropics. Higher climate temperature leads to fluid loss from the skin, and insufficient drinking water causes chronic diarrhea, which further promotes the development of urolithiasis (16). One random study demonstrated that in elderly people aged 60 years or older, urolithiasis was associated with asymptomatic diarrhea (17). The change in the urine pH value might be one of the reasons for this difference. Gastrointestinal disorders can cause urolithiasis through hyperconcentrated acidic urine induced by hyperoxaluria or diarrhea (18). Untreated celiac disease, a malabsorptive

Table 3 Adjusted association of chronic bowel diseases with renal stones, stratified by BMI

Chronic bowel disease	BMI (≤20 kg/m^2)		BMI (>20, ≤25 kg/m^2)		BMI (>25, ≤30 kg/m^2)		BMI (>30 kg/m^2)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
None	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–	1.0 (reference)	–
Chronic constipation								
Crude model†	0.987 (0.096, 10.136)	0.99	0.846 (0.361, 1.982)	0.70	0.871 (0.423, 1.792)	0.71	1.587 (0.987, 2.550)	0.056
Model 1‡	0.918 (0.059, 14.356)	0.95	0.905 (0.375, 2.183)	0.83	0.995 (0.482, 2.054)	0.99	2.098 (1.330, 3.310)	0.004
Model 2§	0.743 (0.025, 21.713)	0.87	0.813 (0.334, 1.977)	0.66	0.971 (0.445, 2.120)	0.94	2.142 (1.389, 3.303)	0.004
Chronic diarrhea								
Crude model†	2.589 (0.390, 17.176)	0.33	1.235 (0.522, 2.924)	0.63	2.615 (1.585, 4.314)	<0.001	1.420 (0.963, 2.093)	0.07
Model 1‡	3.835 (0.658, 22.348)	0.15	1.073 (0.435, 2.651)	0.88	2.615 (1.592, 4.297)	<0.001	1.449 (0.972, 2.160)	0.08
Model 2§	4.831 (0.811, 28.775)	0.10	1.096 (0.447, 2.686)	0.84	2.509 (1.460, 4.312)	0.002	1.406 (0.901, 2.193)	0.15

†, adjusted for none; ‡, adjusted for demographic characteristics (age, gender, race, family income-to-poverty ratio, and education level); §, adjusted for demographic characteristics in model1 and smoking history, alcohol drinking history, recreational activity, diabetes mellitus, blood hypertension, and coronary heart disease. BMI, body mass index; OR, odds ratio; CI, confidence interval.

Table 4 The comparison between complete data analysis and multiple imputation analysis for detection of sensitivity

Chronic bowel disease	Complete data		Multiple imputation	
	OR (95% CI)	P value	OR (95% CI)	P value
None	1.0 (reference)	–	1.0 (reference)	–
Chronic constipation	1.059 (0.755, 1.483)	0.74	1.042 (0.757, 1.433)	0.80
Chronic diarrhea	1.785 (1.365, 2.334)	<0.001	1.527 (1.128, 2.068)	0.006

Adjusted for age, gender, race, family income-to-poverty ratio, education level, body mass index, smoking history, alcohol drinking history, recreational activity, diabetes mellitus, blood hypertension, and coronary heart disease. OR, odds ratio; CI, confidence interval.

disorder, is associated with a high risk of urolithiasis (19).

The symptoms of urolithiasis, especially calcium oxalate nephrolithiasis, are sensitive to gastrointestinal disorders. Gut mucosa absorption affects calcium and oxalate metabolism, thereby promoting the development of hypercalciuria and hyperoxaluria (20). Existing epidemiological observational evidence has demonstrated that IBD, especially Crohn's disease, increases the risk of kidney stones (21). Another nationwide population-based cohort study also indicated that IBD patients have a 2-fold greater risk of urolithiasis, especially patients with Crohn's disease (22). A recent study revealed that the entire gut microbiome was more likely to engage in oxalate absorption and other risk factors for stone formation (23).

The components of the bowel microbiome affect host metabolism and health. Abnormalities in the intestinal microbiome are associated with recurrent kidney stones (24). Recent studies have demonstrated that fecal and urinary microbiota were dysbiosis in patients with renal stones (25,26). A lack of *O. formigenes* colonization is positively associated with kidney stones (27). Diarrhea has long been associated with gut microorganism imbalance. A previous study confirmed that the urinary excretion of oxalate and urea was reduced in probiotic (*Lactobacillus*) pretreated rats. The results indicated that probiotics could help catabolize oxalate to prevent renal stones (28). In contrast, a recent study reported the opposite result. Real-time polymerase chain reaction (PCR) of stool and 24-hour urine samples indicated no significant difference between *Lactobacillus*/*Bifidobacterium* and renal stones (29). However, further studies are needed to determine the function of these microorganisms in the gut. Reducing chronic diarrhea is helpful for maintaining the gut probiotics, which may prevent renal stones.

Notably, a cross-sectional study of the NHANES demonstrated that chronic diarrhea was related to depression (9). Intriguingly, another study suggested that depression indicates a high risk of renal stones (30). The interactions among psychology, bowel status and urolithiasis may provide novel insight. Additional studies regarding the impact of psychogastroenterology on bowel status and renal stones are warranted to clarify the associations among them.

Chronic constipation was not associated with the overall risk of renal stones in this study. Few studies have investigated the association between constipation and urolithiasis. A previous study revealed that hydration is important for maintaining health, in relation to recognition and kidney stones (31). Increased fluid intake, not alkali or oxalate intake, decreases calcium oxalate supersaturation (32). Inversely, irritated bowel disease with constipation is a symptom cluster affected by diverse pathologies including gut microbiota imbalance, immune dysfunction, brain-gut interactions, intestinal permeability changes, and psychosocial status disorders (33). Interestingly, chronic constipation was found to be associated with the risk of kidney stones in participants with BMI over 30 kg/m^2. Studies have indicated that obesity is related to an increased risk of kidney stones (34,35). Furthermore, a cross-sectional study revealed that Crohn's disease patients with visceral obesity had higher incidence of chronic constipation (36). Another study demonstrated that children with constipation were more likely to be overweight. Thus, we speculate that BMI may play an important role in the relationship between chronic constipation and the risk of renal stones (37).

To our knowledge, we comprehensively analyzed the relationships of chronic constipation and chronic diarrhea with renal stones based on the large-scale prospective NHANES dataset, which represents the population in the US. We focused on chronic constipation and diarrhea in the US population. Furthermore, we evaluated the associations after adjustment for critical confounding factors. Our findings are validated by sensitivity analysis.

There were also some limitations in our study. First, the causal link associations could not be obtained on account of the cross-sectional design of the NHANES dataset. Second, the data on renal stones were collected by interview, which might cause recall bias in self-reported data. A large number of participants with incomplete data or asymptomatic urolithiasis were missed. Third, the limited data in the bowel health questionnaire made it difficult to collect more information for bowel health, including abdominal pain and drug application history. Fourth, we could only assess the bowel health status by questionnaire. Chronic bowel diseases are best assessed by using the Rome criteria. Hence, the definition of "chronicity" might be ubiquitous. The duration of the most common stool type was not recorded in the NHANES dataset. Fifth, there were still some unaccounted or unobserved covariates that should be included. Finally, although we conducted a multiple imputation sensitivity analysis, there were still unpredictable biases that influence the findings of our study.

Conclusions

This cross-sectional study indicated that chronic diarrhea is associated with an overall risk of renal stones, especially in participants with BMI of 25–30 kg/m^2 in the US adult population. Chronic constipation is positively related to the risk of renal stones in individuals with BMI over 30 kg/m^2. Public health awareness should be aroused to focus on sustaining bowel health status. These findings should be confirmed by further prospective cohort studies with larger sample size in the future.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-212/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-212/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.

com/article/view/10.21037/tau-24-212/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The research was performed using de-identified data from the publicly National Health and Nutrition Examination Survey dataset. The ethical review board of the National Center for Health Statistics granted approval to the NHANES protocols. Written informed consent was acquired by the NHANES for participating in the survey.

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