

# Decreased renal function among adults with a history of nephrolithiasis: A study of NHANES III

DANIEL L. GILLEN, ELAINE M. WORCESTER, and FREDRIC L. COE

Department of Health Studies and Department of Medicine, University of Chicago, Chicago, Illinois

## Decreased renal function among adults with a history of nephrolithiasis: A study of NHANES III.

**Background.** Although intuitively appealing, the hypothesis that nephrolithiasis is associated with decreased renal function has not thoroughly been investigated. Because the prevalence of nephrolithiasis and chronic renal disease in westernized societies has risen over the past three decades, we sought to determine if persons with a history of kidney stones have lower renal function relative to nonstone formers.

**Methods.** We used data from the Third National Health and Nutrition Examination Survey (NHANES III) to compare estimated glomerular filtration rate (GFR) between persons over age 30 with and without a history of kidney stones. In total, 876 persons with a history of stones, and 14,129 persons without stones were available for analysis.

**Results.** We observed that the association between history of stones and estimated GFR depends on body mass index (BMI) ( $P=0.004$ ). After adjustment for potential confounding factors, mean estimated GFR in stone formers with a BMI  $\geq 27$  kg/m<sup>2</sup> was 3.4 mL/min/1.73 m<sup>2</sup> lower than that of similar nonstone formers (95% CI  $-5.8, -1.1$ ) ( $P=0.005$ ). No difference was found among persons with a BMI  $<27$  kg/m<sup>2</sup>. The probability of an overweight stone former having an estimated GFR between 30 and 59 mL/min/1.73 m<sup>2</sup> relative to a GFR above 90 mL/min/1.73 m<sup>2</sup> was nearly twice that of a similar nonstone former [relative risk ratio (RRR) = 1.87, 95% CI 1.06, 3.30].

**Conclusion.** Among overweight persons, nephrolithiasis may not merely be a disease of stones, but may also reduce kidney function. Further work in alternate study samples is needed to validate this finding and determine the mechanisms responsible.

The impact of chronic renal insufficiency (CRI) on public health has been well documented. The prevalence of elevated serum creatinine ( $>1.5$  mg/dL in men and  $>1.4$  mg/dL in women) in the Framingham Heart Study was estimated at 8.0% for men and 8.9% for women [1], while more than 300,000 persons in the United States have end-stage renal disease (ESRD) [2]. Alarming, the

incidence of CRI is rising throughout the world [3]. With respect to patient outcomes, CRI patients suffer from an increased risk of mortality and cardiovascular disease relative to the general population [4, 5]. Given the number of persons at risk for CRI and the prognosis associated with the disease, identification of risk factors for the development of renal disease has become a top priority to researchers in the nephrology community.

As the incidence of CRI has risen over the past three decades, the frequency of nephrolithiasis in westernized societies has also increased. Recently, the prevalence of nephrolithiasis among 20- to 74-year-old patients in the United States was estimated to be 5.2% during the years 1988 to 1994, compared to 3.8% from 1976 to 1980 [6]. While much is known about the pathogenesis and treatment of nephrolithiasis [7], the clinical consequences of stone disease remain relatively unidentified. In particular, little is known about the effect of stone disease on renal function. Our hypothesis is that repeated transient obstruction from stone passage, treatments such as extracorporeal shock wave lithotripsy (ESWL), and possibly mineral deposits in the renal medulla may damage nephrons and reduce renal function [8–10]. The current study uses national health survey data collected during the years 1988 to 1994 to compare renal function, as measured by estimated glomerular filtration rate (GFR), between persons with and without a history of nephrolithiasis. We hypothesized that stone formers would have lower estimated GFR when compared to similar nonstone formers.

## METHODS

### Study population

Data from the NHANES III was used for this analysis. A detailed description of the methods used in the survey is available elsewhere [11]. Briefly, NHANES III was one of several periodic surveys conducted by the National Center for Health Statistics. The survey, conducted during 1988 to 1994, was designed to provide national estimates of health and nutritional status in the civilian non-institutionalized United States population aged 2 months

**Key words:** nephrolithiasis, kidney stones, glomerular filtration rate.

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and older. Data collected in NHANES III included sociodemographic factors, medical history, health-related behaviors, and medication use. Ultimately, 33,994 persons were interviewed. In the current study, we limit our analysis to adults aged 30 to 90 years with information on the lifetime occurrence of kidney stones ( $N = 15,005$ ). The choice to restrict our analysis to individuals over 30 years of age was based primarily on two factors. First, the prevalence of stones among individuals less than 30 years of age is quite low, yet these individuals carry great sampling weight in the NHANES survey (due to oversampling of the elderly). Thus, any conclusions drawn would be quite heavily influenced by a relatively small number of stone formers in this age group. Second, we hypothesized that the effect of nephrolithiasis on renal function is a cumulative one that may take many years to manifest. Thus by focusing on individuals over 30 years of age, this would provide ample time for the effects of stone disease on renal function to begin to develop.

### Exposure and outcome definitions

The primary exposure in our analysis was any history of kidney stones. All participants over age 30 who answered "yes" to the question "Have you ever had a kidney stone?" ( $N = 876$ ) were considered to have a history of nephrolithiasis. Persons who responded "don't know" ( $N = 13$ ) or did not respond ( $N = 8$ ) were excluded. The outcome of interest was taken to be renal function as estimated by the Modification of Diet in Renal Disease (MDRD) equation [12]. Thus, GFR was estimated as

$$\text{GFR}_{\text{MDRD}} = 170 \times S_{\text{Cr}}^{-0.999} \times \text{age}_{\text{yrs}}^{-0.176} \times \text{BUN}^{-0.170} \\ \times S_{\text{alb}}^{0.318} \times 1.180^{\text{black}} \times 0.762^{\text{female}}$$

where  $S_{\text{Cr}}$  denotes serum creatinine, BUN denotes blood urea nitrogen, and  $S_{\text{alb}}$  denotes serum albumin. Coresh et al [13] have reported that the assay used for measuring serum creatinine in the NHANES study resulted in creatinine levels systematically higher than those used to obtain the MDRD prediction model. As a consequence, they suggest creatinine values from NHANES III be recalibrated to account for an average overestimate of 0.23 mg/dL. All analyses presented here have performed the recommended recalibration.

### Statistical analysis

All reported point estimates and standard errors incorporate the NHANES III survey weights which account for unequal probability of selection into the NHANES sample and survey nonresponse. Variance estimates were computed via the method of linearization [14]. Patient characteristics, adjusted for stone history and age, were compared using linear regression for continuous covari-

ates and logistic regression for categorical covariates. Multiple linear regression was used to compare mean estimated GFR between stone formers and nonstone formers. Covariates identified as potential confounders in the relationship between estimated GFR and stone history were adjusted for. These included age, gender, race (African American vs. other), body mass index (BMI), systolic blood pressure, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), diabetes, history of cardiovascular disease (myocardial infarction, stroke, congestive heart failure), smoking status (ever vs. never), health insurance status, and use of prescription diuretics. Other covariates considered as adjustment variables but not presented here include alcohol use, selected dietary factors, including calcium intake, household income, and marital status. Multiplicative interactions between stone history and age, gender, race, diabetes, and BMI were formally tested. The presented analyses include adjustment for BMI as a continuous linear covariate. However, to address the potential for residual confounding by BMI, secondary analyses adjusting for BMI as a categorical covariate (based upon quintiles of the distribution) were also performed. As these results did not qualitatively change our findings, we have chosen to present models adjusting for BMI as a continuous linear covariate. In addition, a separate linear regression model among persons with a history of stones was conducted to examine the association between prior stone treatment and estimated GFR.

It was a priori hypothesized that stone formers would not merely experience a downward shift in the distribution of GFR, but that the distribution of GFR among stone formers would be skewed to the right, resulting in a higher proportion of persons in the lower-tail of the distribution of GFR. To test this hypothesis, estimated GFR was categorized using cut points suggested by the National Kidney Foundation's Kidney Dialysis Outcomes and Quality Initiative (K/DOQI) guidelines for classification of CRI: less than 30 mL/min per 1.73 m<sup>2</sup>, 30 to 59 mL/min per 1.73 m<sup>2</sup>, 60 to 89 mL/min per 1.73 m<sup>2</sup>, and 90 mL/min per 1.73 m<sup>2</sup> or above [15]. Multinomial logistic regression was used to compare the relative risk of having an estimated GFR in a lower category relative to the highest category between persons with and without nephrolithiasis. Model based estimates are reported as relative risk ratios comparing stone formers with nonstone formers. Adjustment covariates included in the multinomial logistic regression included age, gender, race, BMI, systolic blood pressure, HbA<sub>1c</sub>, diabetes, history of cardiovascular disease, smoking status, health insurance status, and use of prescription diuretics.

All statistical analyses were performed using conventional commercial software (Stata Corp. 2003, Stata Statistical Software, Release 8.0, College Station, TX, USA).

**Table 1.** Age-adjusted population characteristics<sup>a</sup> by history of stone disease

Characteristic	History of renal stones (N = 876)	No history of renal stones (N = 14,129)	P value <sup>b</sup>
Mean age at time of interview years	53.1 (±0.8)	42.3 (±0.4)	<0.001
% Female	38.3 ± 2.6	53.7 ± 0.5	<0.001
% African American	4.0 ± 0.5	10.8 ± 0.7	<0.001
% Smoking (ever vs. never)	63.3 ± 2.5	55.9 ± 0.9	0.006
% Diabetes	6.8 ± 1.0	5.5 ± 0.3	0.191
% Cardiovascular disease <sup>c</sup>	6.4 ± 0.8	4.1 ± 0.3	0.001
% Diuretic use	7.8 ± 10.1	6.2 ± 0.4	0.099
Mean body mass index	27.9 (±0.3)	26.9 (±0.1)	0.006
Mean systolic blood pressure mm Hg	128.2 (±0.9)	126.3 (±0.4)	0.035
Mean diastolic blood pressure mm Hg	78.3 (±0.7)	76.9 (±0.3)	0.076
Mean serum creatinine g/dL	0.91 (±0.020)	0.85 (±0.004)	0.005
Mean glomerular filtration rate (MDRD)	93.1 (±0.9)	95.6 (±0.5)	0.008
Mean urine albumin mg/dL	4.6 (±1.0)	2.7 (±0.2)	0.062
Mean urine creatinine g/dL	0.13 (±0.004)	0.11 (±0.001)	0.241
Treatment for stones			
% Taken medication for stones	40.8 ± 2.9	–	–
% Received ESWL	7.4 ± 1.8	–	–
% Had surgery to remove stones	19.1 ± 2.2	–	–

MDRD is Modification of Diet in Renal Disease; ESWL is extracorporeal shock wave lithotripsy.

<sup>a</sup>Statistics represent either mean or percent ± SE and are weighted to account for the stratified, multistage sampling design of the Third National Health and Nutrition Examination Survey (NHANES III). With the exception of age, all estimates are age-adjusted and represent the estimated mean for a 50-year-old participant.

<sup>b</sup>P values are age-adjusted and account for the stratified sampling design of NHANES III.

<sup>c</sup>Cardiovascular disease defined as any history of myocardial infarction, stroke, or congestive heart failure.

**Table 2.** Linear regression coefficient estimates modeling glomerular filtration rate (GFR) [Modification of Diet in Renal Disease(MDRD)]<sup>a,b</sup> stratified by body mass index (BMI)

Covariate	BMI <27 Coefficient		BMI ≥27 Coefficient	
	(95% CI)	P value	(95% CI)	P value
History of renal stones (yes vs. no)	1.6 (–1.4, 4.5)	0.287	–3.4 (–5.8, –1.1)	0.005
Age (per 5 years)	–3.6 (–3.8, –3.3)	<0.001	–3.8 (–4.1, –3.4)	<0.001
Gender (female vs. male)	0.3 (–1.4, 2.1)	0.697	1.2 (–1.0, 3.4)	0.279
Race (African American vs. other)	10.7 (8.4, 12.9)	<0.001	7.9 (6.4, 9.4)	<0.001
BMI (per kg/m <sup>2</sup> )	–0.7 (–1.1, –0.3)	0.001	–0.1 (–0.3, 0.1)	0.225
Systolic blood pressure (per 10 mm Hg)	0.5 (0.1, 0.9)	0.024	–0.7 (1.3, –0.1)	0.016
Diuretic use (yes vs. no)	–8.1 (–11.0, –5.1)	<0.001	–6.2 (–8.5, –4.0)	<0.001

<sup>a</sup>All estimates are weighted to account for the stratified, multistage sampling design of the Third National Health and Nutrition Examination Survey (NHANES III) and are adjusted for history of stones, age, gender, race, BMI, and systolic blood pressure, diabetes, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), cardiovascular disease (myocardial infarction, stroke, congestive heart failure), smoking status (never, former, current), health insurance, and diuretic use.

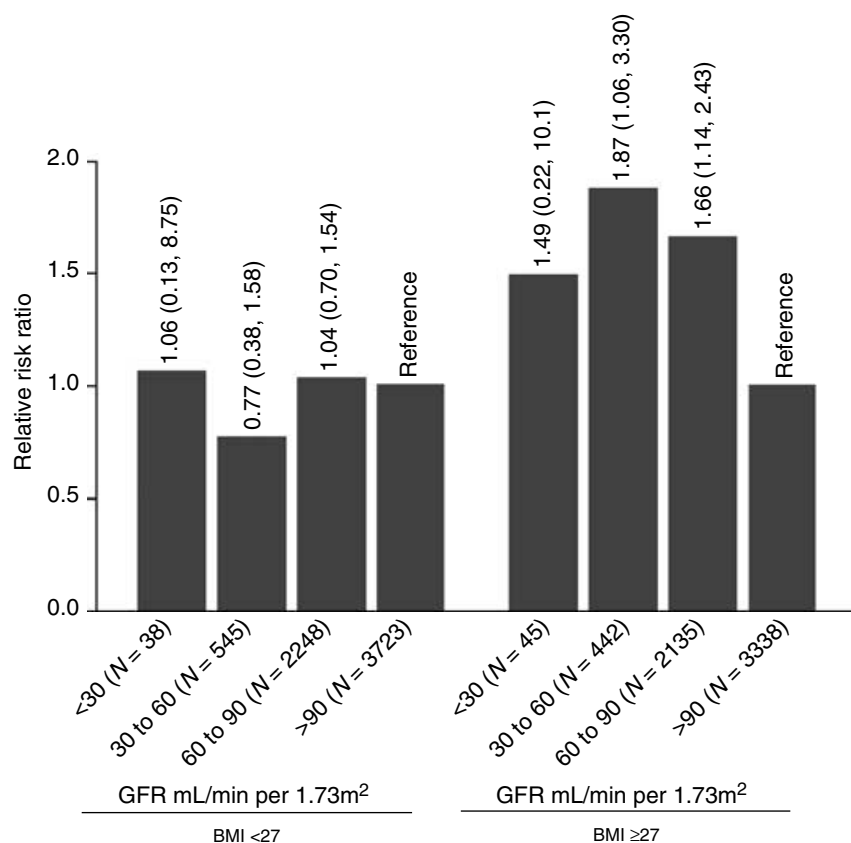
<sup>b</sup>Interaction between renal stones and BMI was statistically significant ( $P = 0.004$ ). Among those with a BMI <27 kg/m<sup>2</sup>, 395 persons had a history of kidney stones and 6671 did not. Among those with a BMI ≥27 kg/m<sup>2</sup>, 395 persons had a history of kidney stones and 5981 did not.

## RESULTS

Table 1 displays age adjusted characteristics of the study sample extrapolated to the noninstitutionalized United States population using sample weights provided by NHANES. Displayed means represent the weighted average of each covariate for an individual of age 50 (the approximate overall mean age of the study sample). After exclusion for missing stone history, 15,005 persons were available for analysis (14,129 nonstone formers and 876 stone formers). After adjustment for age, persons with a history of kidney stones tend to be male, non-African American, heavier, more likely to have smoked, more likely to have had prior cardiovascular disease, and have higher blood pressure. After adjustment for age it was estimated that stone formers have lower mean estimated GFR (and higher mean serum creatinine) than nonstone formers (93.1 mL/min per 1.73 m<sup>2</sup>

vs. 95.6 mL/min per 1.73 m<sup>2</sup> for an individual of age 50) ( $P = 0.008$ ). Among stone formers, approximately 41% received medication for their stones, 7% underwent ESWL therapy, and 19% underwent surgery to remove a stone.

Multiple linear regression results modeling estimated GFR as a function of stone history with adjustment for age, gender, race, BMI, systolic blood pressure, HbA<sub>1c</sub>, diabetes, cardiovascular disease, smoking, insurance status, and use of diuretics are presented in Table 2. A significant interaction between stone history and BMI was detected at the analysis stage ( $P = 0.004$ ), indicating that the association between stone history and estimated GFR is dependent upon body size. As a result, all remaining analyses presented are stratified by BMI level (<27 kg/m<sup>2</sup> vs. ≥27 kg/m<sup>2</sup>). A BMI of 27 kg/m<sup>2</sup> was chosen as a stratification cut point because it represented the



**Fig. 1. Model-based estimates of the relative risk ratio comparing persons over age 30 with a history of kidney stones to those without.** Each estimate is weighted to account for the stratified, multistage sampling design of the Third National Health and Nutrition Examination Survey (NHANES III) and is interpretable as the relative risk of having a glomerular filtration rate (GFR) in one category relative to having a GFR in the reference category among persons with a history of kidney stones divided by the similar relative risk in those with no history of kidney stones. All estimates are adjusted for age, gender, race, body mass index (BMI), systolic blood pressure, diabetes, hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>), cardiovascular disease (myocardial infarction, stroke, congestive heart failure), smoking status (never, former, current), health insurance, and diuretic use.

estimated median BMI of stone formers in the sample. Among persons with a BMI less than 27 kg/m<sup>2</sup>, history of stone disease was not found to be associated with estimated GFR (adjusted mean difference = 1.6; 95% CI -1.4, 4.5) ( $P = 0.287$ ). However, among individuals with a BMI  $\geq 27$  kg/m<sup>2</sup>, stone formers were found to have an estimated GFR 3.4 mL/min per 1.73 m<sup>2</sup> lower on average when compared to nonstone formers (95% CI -5.8, -1.1) ( $P = 0.005$ ). Additional analyses comparing mean estimated GFR between stone formers and nonstone formers within categories of obesity as defined by the World Health Organization (WHO) (BMI <25 kg/m<sup>2</sup>, BMI between 25 and 30 kg/m<sup>2</sup>, and BMI >30 kg/m<sup>2</sup>) [16], were also conducted. These analyses again suggest a reduction in GFR among stone formers with a high BMI. After adjustment for those potential confounding factors listed above, the mean difference in estimated GFR comparing stone formers to nonstone formers was calculated to be 1.7 (95% CI -2.2, 5.5) ( $P = 0.385$ ), -1.4 (95% CI 3.3, 0.5) ( $P = 0.138$ ), and -3.5 mL/min per 1.73 m<sup>2</sup> (95% CI -6.7, -0.2) ( $P = 0.040$ ) among persons with a BMI less than 25, between 25 and 30, and greater than or equal to 30 kg/m<sup>2</sup>, respectively.

Figure 1 displays model-based relative risk ratio (RRR) estimates comparing the probability of low estimated GFR relative to an estimated GFR greater than

90 mL/min per 1.73 m<sup>2</sup> between stone formers and nonstone formers. No association was found between stone history and estimated GFR among nonoverweight individuals. However, among individuals with a BMI greater than 27 kg/m<sup>2</sup>, there exists an association between stones and renal function. Relative to having an estimated GFR greater than 90 mL/min per 1.73 m<sup>2</sup>, the odds of having an estimated GFR less than 30, 30 to 59, and 60 to 89 mL/min per 1.73 m<sup>2</sup> were estimated to be 1.49-, 1.87-, and 1.66-fold higher among persons with a history of stones when compared to those without, respectively. Although the RRR comparing the lowest estimated GFR group to the highest was not found to be statistically significant, the RRR associated with the other two categories was significantly greater than 1 ( $P = 0.030$  and  $P = 0.010$ , respectively).

Given potential imperfections in our estimate of GFR, secondary analyses modeling log-serum creatinine were also performed and similar associations were found. In addition, subanalyses among persons with a history of stone disease were conducted to determine if stone treatment is associated with lower estimated GFR (results not shown). After adjustment for those confounders considered above, surgery, ESWL, nor the use of stone medications was found to be significantly associated with reduced GFR.

## CONCLUSION

Using a nationally representative sample, we found that among overweight persons, stone formers had lower estimated GFR when compared to similar nonstone formers. Further, the probability of an overweight stone former having an estimated GFR between 30 and 59 mL/min/1.73 m<sup>2</sup> relative to a GFR above 90 mL/min/1.73 m<sup>2</sup> was observed to be nearly twice that of a similar nonstone former. However, no significant differences in estimated GFR comparing stone formers to nonstone formers were observed among persons with a BMI less than 27 kg/m<sup>2</sup>. These findings imply that among overweight individuals, nephrolithiasis may not simply be a disease of stone formation in the collecting system but also involves the kidneys in ways that lead to decreased nephron number or function.

Our finding that a history of stones is associated with lower estimated GFR among persons with a BMI greater than 27 kg/m<sup>2</sup> may be attributable to many factors. First, it has been shown that formation of calcium oxalate stones is associated with the deposits of apatite particles in the basement membranes of the thin loops of Henle and in the deep medullary interstitium [10]. Although interstitial inflammation and fibrosis, and tubule cell injury and loss were not prominent, the particles achieve high densities in some regions and certainly could cause nephron injury. Also, stone passage itself causes transient obstruction, and obstruction is a well established initiator of renal damage. Finally, ESWL causes renal injury in experimental animals, and may result in a loss of renal function among humans. Although most clinical studies suggest that initial declines in GFR improve with time [17], long-term effects are unknown. Although we did not observe differences in estimated GFR due to stone treatment, our data were limited with respect to treatment history (neither duration and dose of medication nor numbers of surgeries or ESWL were collected in NHANES), and given the limited number of individuals having undergone therapy our analysis was not adequately powered to investigate this association.

We observed an association between stone history and decreased GFR only among overweight individuals (BMI >27 kg/m<sup>2</sup>). At least two possible explanations for this differential effect exist. First, stone type may be associated with reduced GFR and higher body weight. Both struvite stones and uric acid stones are associated with a greater loss of renal function when compared to other stone types [18–21], and are also associated with higher body weight. These associations may partially explain the interaction between BMI and stone history that was observed in our analysis. However, these stone types account for no more than 20% of stones, overall. An additional explanation may be that renal hemodynamics are altered in heavier individuals; higher BMI has been as-

sociated with an increase in filtration fraction [22]. This could raise intraglomerular pressure, and increase susceptibility to renal damage. Renal hemodynamic changes return to normal following weight loss [23]. This hypothesis is supported by studies finding that obesity is a risk factor for decreased GFR in various conditions [24–28]. Moreover, elevated BMI has been found to predict new onset kidney disease in a recent longitudinal study [29]. Therefore, if kidney stone disease results in some absolute loss of nephrons, overweight individuals may experience a greater loss of kidney function with time.

Our study does suffer from limitations. First, we are limited in our ability to adequately estimate an association between stone history and renal function in young adults due to a lack of data on stone formers less than age 30. Further data on young stone formers are needed to address this issue; however, this should not affect the results found among older stone formers. Next, we did not have information on the total number or type of stones for individuals. Although this data may have been helpful in further investigating the link between stone disease and reduced GFR, it was not necessary for establishing an association between stone history and GFR. It is unlikely that perfect classification of the exposure of interest was attained in the NHANES survey. With this said, the study is not likely to suffer from recall bias since kidney stones are painful and rarely mistaken for any other disease. Thus any misclassification in the study would likely be nondifferential and would only result in an underestimation in the magnitude of the association between stone history and GFR. Finally, since this is an observational study there is the potential for unmeasured confounders. One example is the use of thiazides, as they are commonly prescribed in the stone-forming population and have been linked to reduced GFR. Although specific information on the use of thiazides is not available in NHANES, we were able to adjust for use of any prescription diuretics, which did not change the results of the analysis. In addition, limited data on dietary factors previously linked to stone formation, such as calcium intake [6], were available from NHANES via 24-hour recall. Secondary analyses adjusting for dietary factors also did not affect the presented results.

Our findings indicate that nephrolithiasis may be associated with nephron damage in a significant number of individuals. That an increased BMI may potentiate renal damage in this setting is important, as persons with stones tend to be heavy. Further work in alternate study samples is needed to validate this finding and to determine the mechanisms for the association between kidney stones and decreased GFR. However, this is the first study to show such a connection in a nationally representative sample of the United States population. Given our observations, the serious nature of renal disease and

the increasing incidence of nephrolithiasis in the United States, further investigation is warranted.

Reprint requests to Daniel Gillen, Ph.D., 5841 South Maryland Ave., MC 2007, Department of Health Studies, The University of Chicago, Chicago, IL 60637.

E-mail: dgillen@health.bsd.uchicago.edu

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