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Nephrolithiasis and Chronic Kidney Disease

ASN Renal Week November 20, 2010

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Division of NEPHROLOGY & HYPERTENSION

Questions we will address

- What is the evidence for increased risk of CKD with kidney stones?
- Are stone formers at increased risk for ESRD?
- What subgroup of stone formers have the most risk of CKD?
- Is the risk of CKD and ESRD limited to only certain types of stone formers (rare genetic diseases, struvite)?
- Are asymptomatic (incidental radiographic) stone formers at risk for CKD?

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Evidence of increased risk of CKD with kidney stones

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Increased risk of kidney stone history in incident CKD patients compared to community controls

- Cases: Newly diagnosed CKD by ICD9 codes and confirmed by two or more elevated SCr levels >1.5 mg/dl (n=548).
- Controls: Random digit dialing and Medicare recipient listings frequency matched to cases on age, sex, race, location (n=514).
- History of nephrolithiasis by chart review in cases and by interview in controls.
- CKD risk was predominantly interstitial nephritis (pyelonephritis)

	N cases (% stones)	OR	(95% CI)
Chronic renal disease (all)	548 (16.8)	1.9	(1.1, 3.4)
Nephrosclerosis	104 (12.5)	1.1	(0.4, 3.0)
Diabetic nephropathy	108 (14.8)	2.5	(0.9, 7.0)
Glomerulonephritis	76 (11.8)	0.8	(0.3, 2.5)
Interstitial nephritis	106 (27.4)	3.4	(1.5, 7.4)
ESRD	36 (13.9)	1.5	(0.3, 8.8)
Renal insufficiency	118 (17.0)	1.1	(0.4, 2.9)

Non-HTN OR=3.0 (1.3,6.8)

HTN OR=1.0 (0.4,2.4)

Vupputuri S et al, AEP, 2004

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eGFR lower for stone formers in the general population with BMI>27

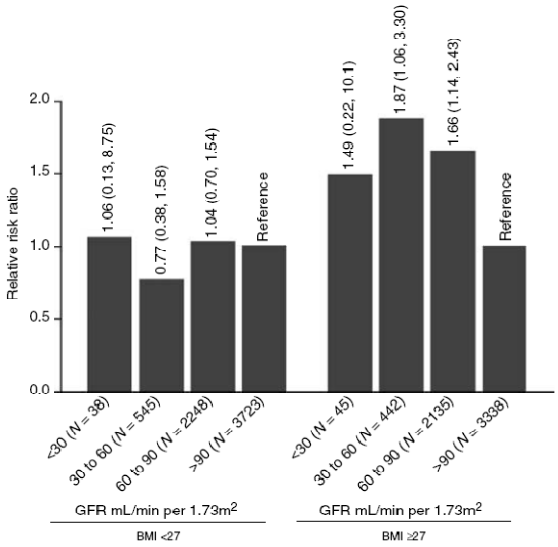
- NHANES III sample

-5.7% stone formers

-Adjusted for age, sex, race, BP, diuretics

-For BMI >27: eGFR lower in stone formers (-3.4 ml/min/1.73 m^2) (p=0.005)

-For BMI <27: No difference (p=0.29)



Gillen DL et al, Kidney Int, 2005

Population-based studies of kidney stones as risk factors for CKD

- Risk factor for CKD in Thailand
- 3459 subjects surveyed with concurrent eGFR and UACR measures
- 5% reported a history of kidney stones
- 18% had CKD (eGFR<60 or UACR>30 **or RBC >5/HPF**)
- Multivariable adjusted OR = 2.7 (95% CI: 1.6 to 4.7)
- Adjusted for age, sex, diabetes, hypertension, & serum uric acid

Ingsathit et al, NDT, 2010

Rochester Epidemiology Project

- Unique and unparalleled records linkage infrastructure for research
  - Data on 753,399 Olmsted County people
    - Linking together 1,454,337 individual patient records
    - Containing over 12,967,559 Outside Source diagnoses
  - Data from 40 outside sources
    - Primary sources: Mayo, Olmsted Medical Center Clinic and Hospital, Rochester Family Medicine Clinic
    - Full List of REP data sources with timeframes can be found at: Data Covering 1935-Present
- **95% of the Olmsted County population has at least one clinic visit every 2-3 years allowing nearly complete enumeration of the local population!**

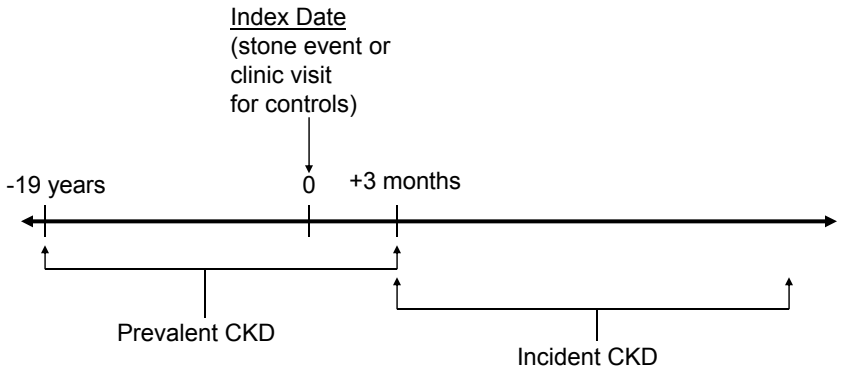
Melton et al, Mayo Clin Proc, 1996

Risk of CKD with kidney stones (matched cohort study design)

- Identified all Olmsted County, MN residents with their first (incident) kidney stone between 1984 and 2003.
  - Stone formers by ICD-9 codes (n=5081): 592, 594.11, and 274.11.
  - Controls matched (3:1) (n=14,144) on:
    - Age and Sex
    - Length of medical record
    - Clinic visit at time of stone event (baseline date)

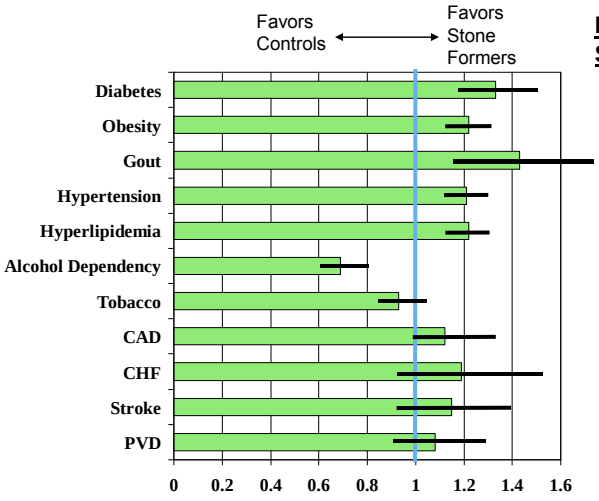
Rule et al, CJASN, 2009

Prevalent versus incident CKD based on a clinical diagnosis



Prevalent Co-morbidities

(based on ICD9, HICDA, and Berkson codes)



	Incident Stone Formers	Controls
Diabetes	9.6%	7.4%
Obesity	24.3%	20.9%
Gout	3.4%	2.4%
Hypertension	19.9%	17.0%
Hyperlipidemia	21.4%	18.3%
Alcohol Dependency	5.5%	7.8%
Tobacco	14.8%	15.7%
CAD	7.4%	6.7%
CHF	2.3%	1.9%
Stroke	3.1%	2.8%
PVD	4.6%	4.3%

Rule et al, CJASN, 2009

Prevalent CKD (clinical diagnosis)

CKD timing prior to index date	Stone Former	Controls	Odds Ratio	95% CI
No prior CKD	4746 (93.3%)	13713 (96.9%)	**1.00**	NA
> 5 years prior	73 (1.44%)	170 (1.20%)	**1.20**	0.91, 1.58
1 to 5 years prior	76 (1.50%)	157 (1.11%)	**1.35**	1.03, 1.78
0 to 1 years	46 (0.90%)	47 (0.33%)	**2.74**	1.82, 4.12
0 to 90 days *after index date*	142 (2.79%)	60 (0.42%)	**6.75**	4.98, 9.14
Overall Prior CKD	337 (6.63%)	434 (3.07%)	**2.24**	1.94, 2.60

Rule et al, CJASN, 2009

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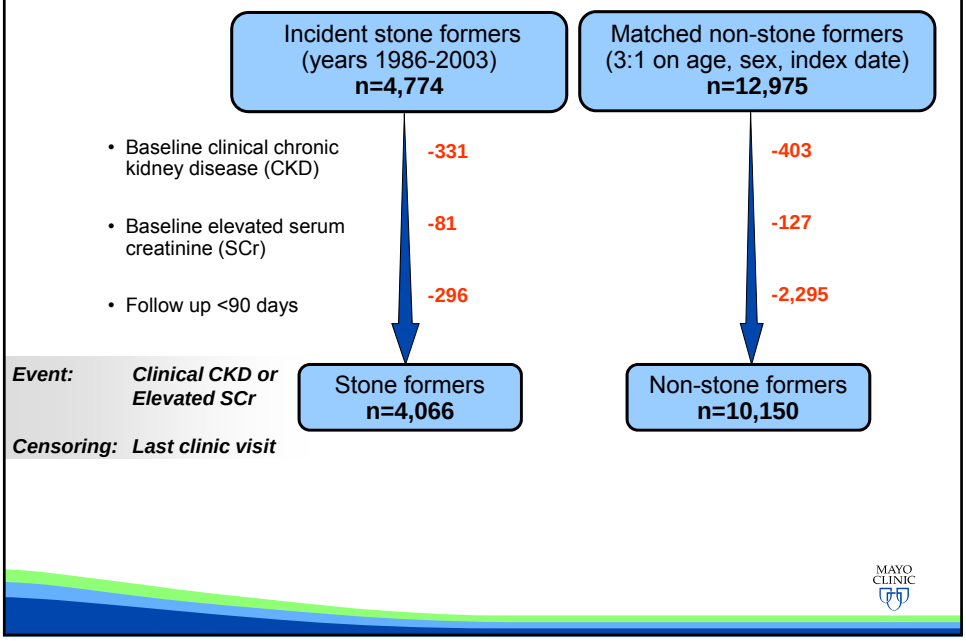

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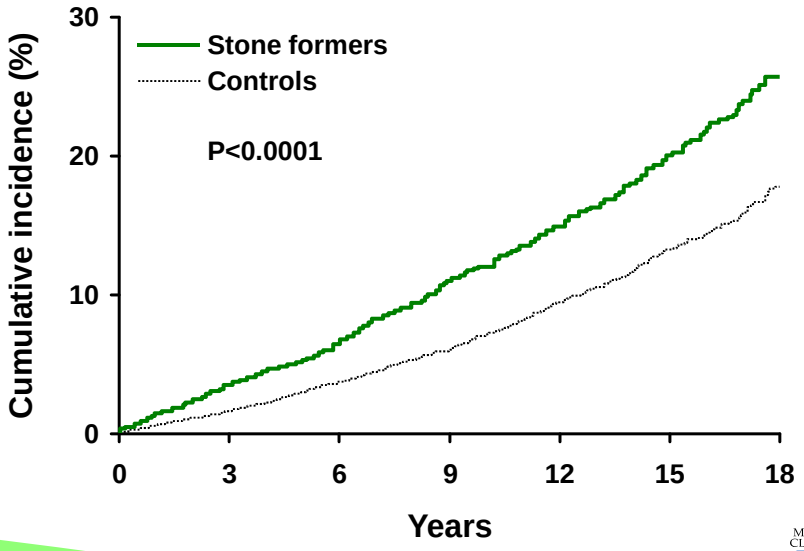
Risk of CKD (clinical diagnosis-ICD9)



Rule et al, CJASN, 2009

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Risk of clinically diagnosed CKD in stone formers adjusting for baseline & time-dependent co-morbidities

Adjusting factors	HR	95% CI	P-value
Unadjusted	1.66	1.49, 1.86	<.0001
age, sex, Diabetes	1.66	1.48, 1.85	<.0001
age, sex, Obesity	1.65	1.48, 1.85	<.0001
age, sex, Essential Hypertension	1.63	1.46, 1.82	<.0001
age, sex, Gout	1.65	1.48, 1.85	<.0001
age, sex, Tobacco Use	1.68	1.50, 1.87	<.0001
age, sex, Coronary Artery Disease	1.62	1.45, 1.81	<.0001
age, sex, Cerebral Infarct	1.66	1.49, 1.85	<.0001
age, sex, CHF	1.64	1.47, 1.84	<.0001
age, sex, Alcohol Dependency	1.68	1.51, 1.88	<.0001
age, sex, Hyperlipidemia	1.63	1.46, 1.82	<.0001
age, sex, Peripheral Vascular Disease	1.65	1.48, 1.85	<.0001
fully adjusted	1.60	1.43, 1.79	<.0001

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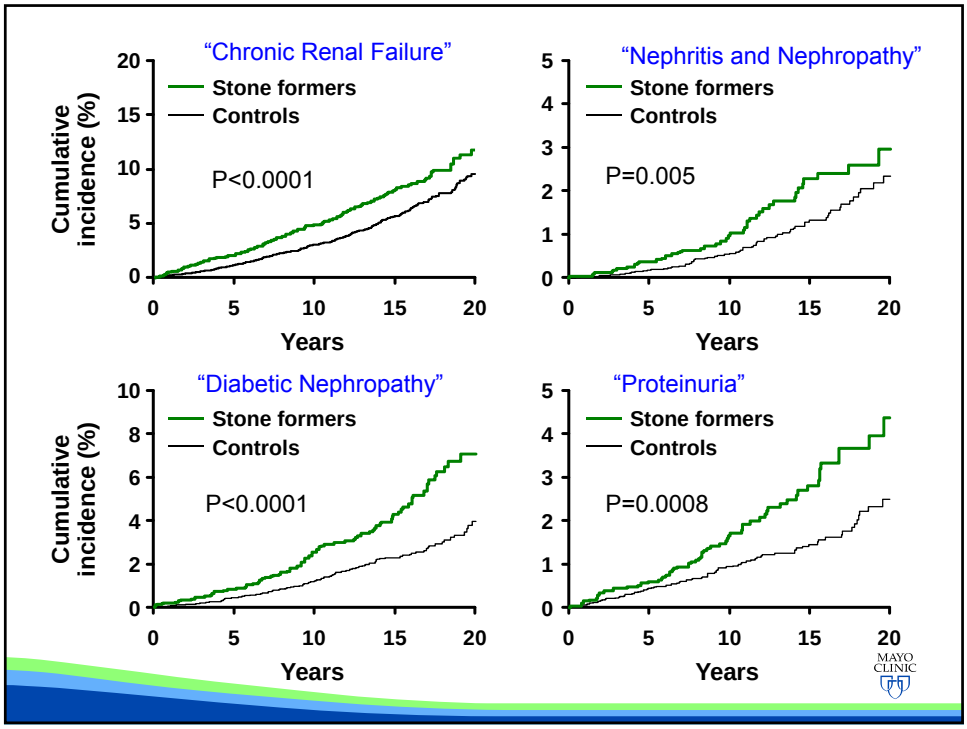
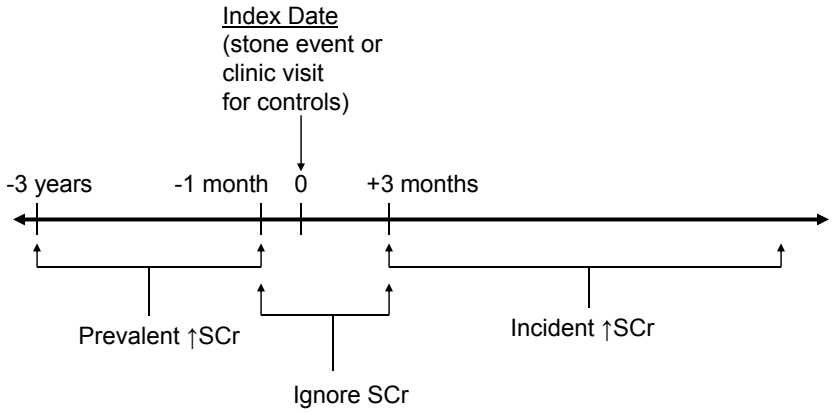


Prevalent versus incident CKD based on SCr



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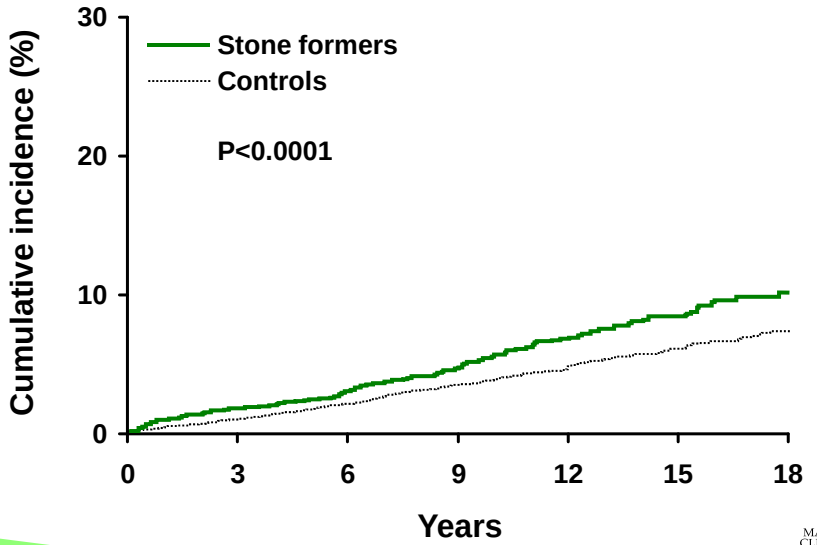
Risk of Sustained ↑SCr (>1.3 M, >1.1 F)



Rule et al, CJASN, 2009

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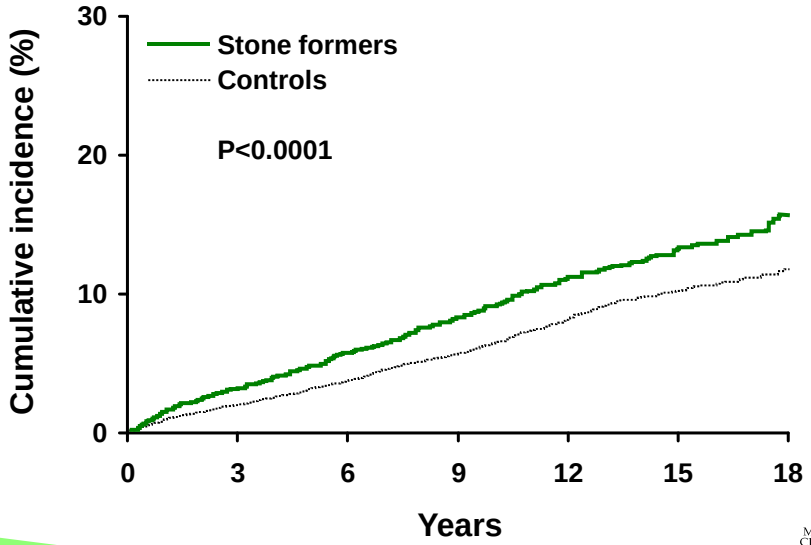
Risk of Sustained eGFR<60 ml/min/1.73 m²



Rule et al, CJASN, 2009

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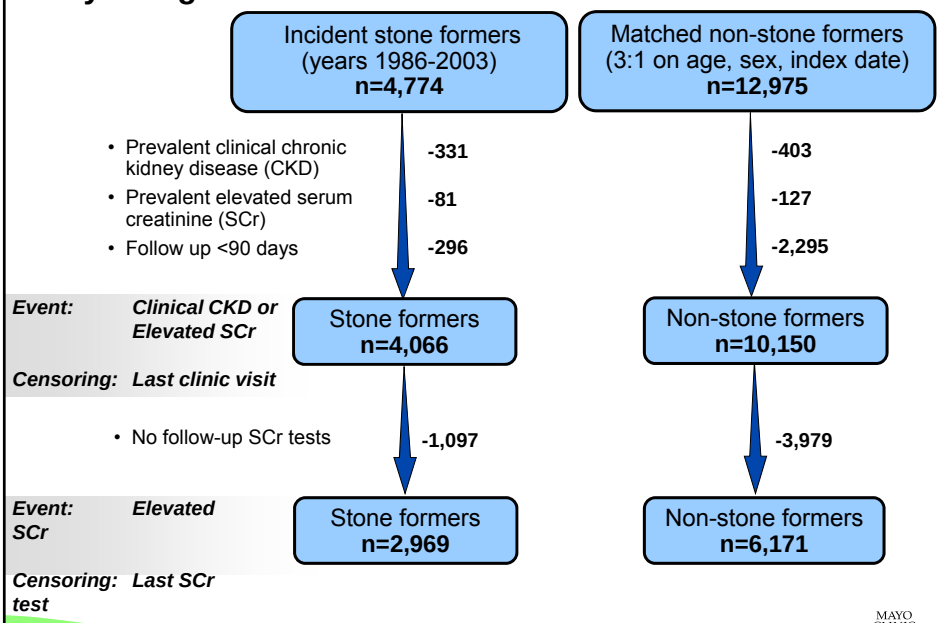
Study Design



Risk of CKD with kidney stones independent of co-morbidities

CKD Definition	Unadjusted HR (95%CI)	Co-morbidity Adjusted HR (95%CI)
Clinical CKD by Diagnostic code	1.67 (1.48, 1.88)	1.56 (1.39, 1.77)
Clinical CKD by Diagnostic code *Limited to persons with follow-up SCr levels*	1.59 (1.41, 1.80)	1.31 (1.10, 1.57)
Sustained elevated SCr	1.46 (1.22, 1.74)	1.36 (1.13, 1.62)
Sustained elevated SCr *Limited to persons with follow-up SCr levels*	1.26 (1.05, 1.51)	1.25 (1.04, 1.49)

Trade-off between a detection bias or a selection bias.

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Evidence of an increased risk of ESRD with kidney stones

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Population-based study of kidney stones as risk factors for ESRD

- Risk factors for incident CKD in England & Wales
- QResearch Database (775,091 women in clinical database)
- 0.7% had kidney stones by diagnosis/procedure at baseline
- CKD defined by ESRD or eGFR<45 or proteinuria
- CKD Incidence 58/10,000 women-yrs
  - Multivariable adjusted Risk of CKD: HR=1.3 (95% CI 1.1 to 1.5)
- ESRD incidence 3/10,000 person-yrs
  - Multivariable adjusted Risk of ESRD: HR=2.1 (95% CI 1.3 to 3.2)
- No independent risk of CKD or ESRD with stones in men

Hippisley-Cox et al, BMC Fam Prac, 2010

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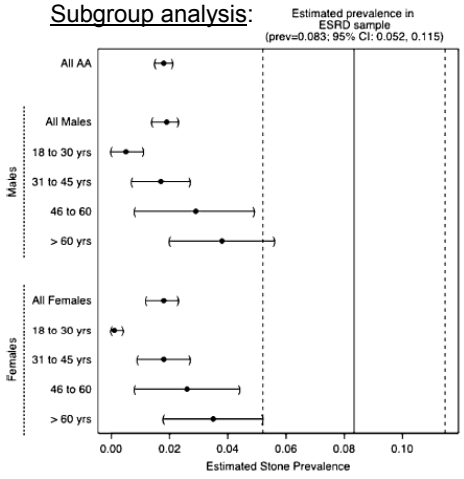
History of kidney stones more prevalent in African Americans with ESRD

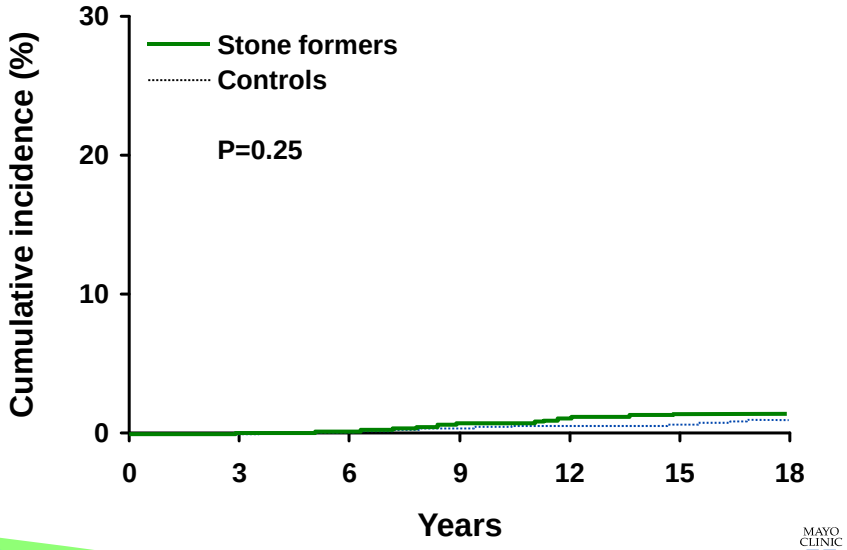
- Cases: 300 African Americans undergoing outpatient hemodialysis at the University of Chicago
- Controls: 5,341 African Americans participating in NHANES III national survey.
- Exposure: "Have you ever had a kidney stone?" on a questionnaire
- Results:
  - Prevalence of kidney stones:
    ESRD: 8% vs Controls: 3% (p<0.001)
  - Of the 25 ESRD patients with stones:
    - 5 had a stone episode within 3 years of starting dialysis
    - 2 had ESRD Attributed to stones
    - No staghorn, primary hyperoxaluria, cystinuria, or bowel disease stones

Subgroup analysis:



Stankus N et al, Urol Res, 2007

End-Stage Renal Disease (Dialysis, Transplant, or Death with CKD)



Rule et al, CJASN, 2009

Risk of ESRD revisited

- Prior analysis relied on internal databases for ESRD and excluded baseline CKD.
- Repeated analysis USRDS database and internal ESRD databases with chart review (92 events).
- Incidence of ESRD

  Stone formers: 1.0 (95% CI: 0.7 to 1.4) events per 1000 person-years

  Controls: 0.5 (95% CI: 0.4 to 0.7) events per 1000 person-years
- Age-sex-adjusted HR=1.9 (95% CI: 1.3 to 2.9)
- Fully-adjusted HR=1.8 (95% CI: 1.2 to 2.7)
- Of the 41 stone formers who developed ESRD, only 3 had kidney stones as primary cause

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ESRD attributed to kidney stones

- Sample: 1391 consecutive ESRD patients from 1989 to 2000 (Paris, France)
- ESRD attributed primarily to kidney stones in 3.2% (n=45)
  - Struvite stones in 42% (n=19)
  - Calcium stones in 27% (n=12)
    - 4 severe hypercalcuria
    - 2 primary hyperparathyroidism with nephrocalcinosis
    - 5 medullary sponge kidney with hypercalcuria
    - 2 recurrent UTIs
    - 1 distal RTA (sjogren's)
  - Uric acid stones in 18% (n=8)
  - Hereditary stones in 13.3% (n=6)
    - 4 primary hyperoxaluria
    - 2 cystinuria
- Solitary functioning kidney in 40% (n=18)

Jungers P et al, AJKD, 2004

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Risk of CKD by stone type

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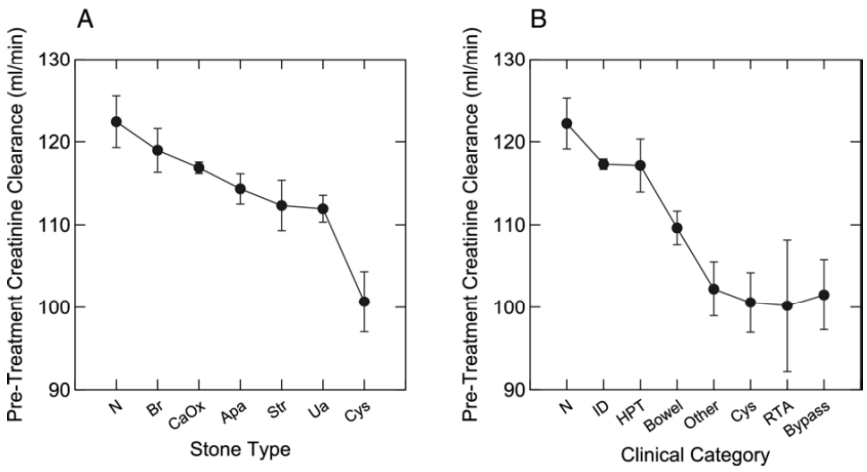
Creatinine clearance lower in stone former (n=1856) compared to normals (n=153)



Worcester EM et al, J Urol, 2006

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Nested Case/Control study with in stone former cohort

- What type of stone formers are at increased risk of CKD?
- 53 stone formers with CKD matched to 106 controls without CKD.
- Hypertension, diabetes, frequent UTIs, struvite stones, and allopurinol use were associated with CKD.
- **Stone type unknown in 50% of community stone formers**
- Number of stone episodes and surgical procedures not associated with CKD
- Study was had limited power (could only detect OR > 3)

Saucier NA et al., AJKD, 2009

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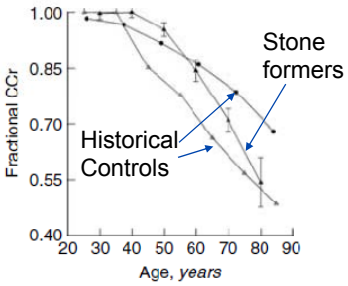
Kidney loss in stone formers

- Sample: 3266 stone formers at a stone clinic (Univ. of Chicago)
- 115 (3.5%) had loss of function in one kidney:
  - 29% from stones (staghorn or high burden)
  - 23% from infection
  - 21% from obstruction
- More rapid decline in urinary creatinine clearance with age in stone formers over age 45 years.



Worcester E et al, Kidney Int, 2003

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Asymptomatic stone formers

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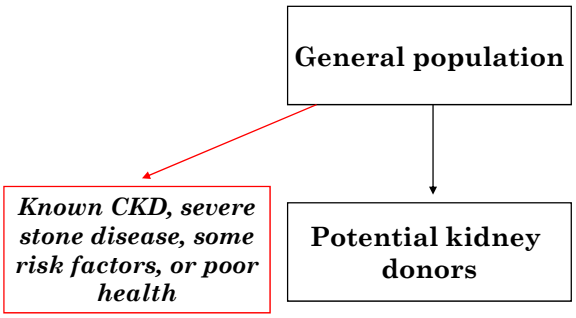

Kidney Measurements Available

- Serum Creatinine
- Urine albumin (spot)
- ESRD
- Symptomatic stones

- GFR (iothalamate)
- CT Angio/urogram (Asymptomatic stones)
- 24-h urine studies
- Ambulatory BP

Restricted range of pathology (similar to healthy volunteer bias), but potentially more valid measurements for renal injury

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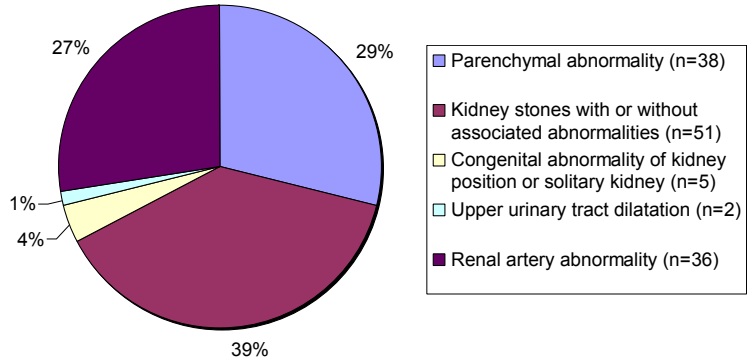
Kidney stones may be the most common incidental radiological abnormalities that contribute to potential kidney donor exclusion

n=132



Lorenz E et al., CJASN, 2010

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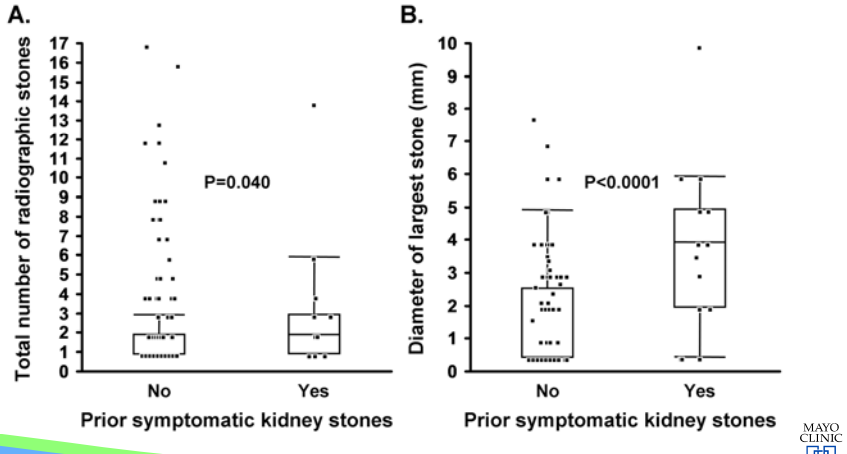
-1957 potential kidney donors
-53 (3%) past symptomatic stones
-25 had radiographic stones
-185 (10%) had radiographic stones only
-1719 (87%) had no evidence of stones
-Among persons with radiographic stones, past symptomatic stones were predictive of more stones and of larger stones:



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Kidney stones and kidney function/morphology

	Group 1: No radiographic or past symptomatic stones (N=1719)	Group 2: Asymptomatic radiographic stones only (N=185)	Group 3: Past symptomatic stones (N=53)	P-value	
Kidney function measure	Mean or %	Mean or %	Mean or %	Group 1 vs 2	Group 1&2 vs 3
GFR, ml/min/1.73 m^2	101	102	102	0.29	0.60
24-h urine alb >15 mg	9.0%	11%	23%	0.49	**0.0007**
24-h urine alb >30 mg	3.5%	3.6%	13%	0.96	**0.0002**
Focal scarring	2.9%	8.1%	11%	**0.0002**	**0.002**
Parenchymal thinning	0.6%	2.7%	1.9%	**0.004**	0.42

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Population based study of radiographic stones and CKD

- Risk factors for CKD in China
- 2596 subjects randomly recruited for a survey
  with eGFR and UACR measures
- 2.2% had kidney stones **by ultrasound**
- 12% had CKD (eGFR<60 or UACR>30)
- Prevalence of sonographic kidney stones:
  - CKD 5.6%,
  - No CKD 1.7%
  - Multivariable adjusted OR=2.9 (p=0.02)

Chen et al, NDT, 2009

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Conclusion

- As a group, symptomatic stone formers are at increased risk of developing CKD and ESRD.
- Nephrolithiasis and CKD share many of the same risk factors (hypertension, diabetes, obesity, hyperuricemia) but there is an association independent of these risk factors.
- The risk of CKD varies by type of kidney stone.
  - Rare genetic diseases and struvite stone formers clearly have increased risk.
  - It is unknown if common calcium stone formers with infrequent episodes have an increased risk.
- Unlike symptomatic stone formers, persons with small incidental asymptomatic stones may not have the same risk of CKD.

Acknowledgments

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- Cynthia Nosek
- Tamara Ellefson-Briske

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- Samuel Edeh

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- Jeremy Palbicki

Characteristics of radiographic vs symptomatic stone formers

- 11% (n=210) of potential donors had radiographic stones
  - Age >45 y 11%, ≤45 y 10% (p=0.62)
  - Men 11%, Women 11%, (p=0.80)
  - Whites 11%, Other 7% (p=.023)
- 2.7% (n=53) had past symptomatic stones
  - Age >45 y 3.9%, ≤45 y 1.7% (p=0.003)
  - Men 3.4%, Women 2.2% (p=0.12)
  - Whites 2.9%, Other 2.4% (p=0.74)

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Validation of stone former classification by dx codes

- 1698 charts of Olmsted County stone formers by diagnostic code (1984-2003) reviewed over 5/09 to 9/10
  - 848 (50%) were incident symptomatic stone formers with radiographic or clinical evidence of a stone.
  - 288 (17%) were prevalent (prior to Olmsted County or 1984)
  - 245 (14%) suspect stone formers (clinical diagnosis)
  - 124 (7%) were asymptomatic radiographic stones
  - 63 (4%) were bladder stones only
  - 134 (8%) Not valid - nothing to suggest stone disease
  - Conversely, 92% have "urolithiasis"
- Had only planned to review 1000 charts from 1984-1990.
- Added another nurse abstractor to target all 4900 charts (Currently reviewing 180 charts per month).

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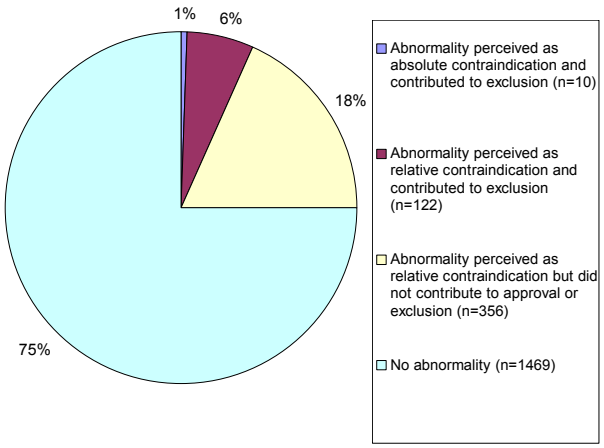
Prevalence of radiographic abnormalities of the renal arteries or kidneys and their impact on approval for donation (n=1957)



Lorenz E et al., CJASN, 2010

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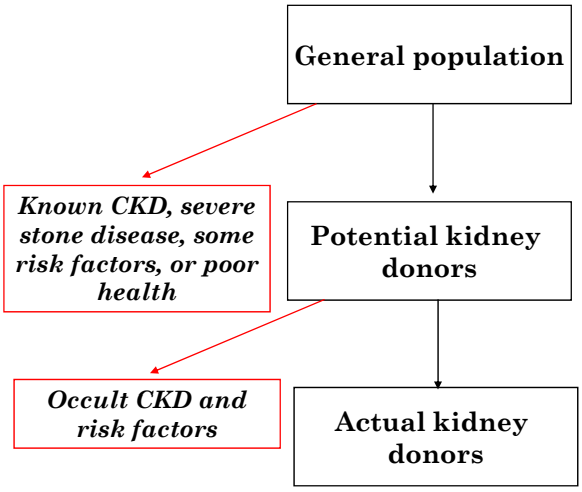

Kidney Measurements Available

- Serum Creatinine
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- ESRD
- Symptomatic stones

- GFR (iothalamate)
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- 24-h urine studies
- Ambulatory BP

- Renal Histology → 'Nephrosclerosis'

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An operational definition for 'nephrosclerosis' in kidney donors

- Determined number of different microstructures in the renal cortex with abnormalities:
  - **Glomeruli (any global sclerosis)**
  - **Tubules (any atrophy)**
  - **Interstitium (fibrosis >5%)**
  - **Arteries (any arteriosclerosis)**
- Sclerosis score **= sum of abnormalities (0-4)**
- Nephrosclerosis **= 2 or more different abnormalities**

Rule AD et al, *Ann Intern Med*, 2010

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Sclerosis score by age group

Rule AD et al, *Ann Intern Med*, 2010

Kidney stones and renal histology

- 1159 actual kidney donors with implantation renal biopsies (manually reviewed)
- 107 (9.4%) had radiographic stones (CT scan)
- 21 (1.8%) have past symptomatic stones
- Urine albumin excretion and nocturnal blood pressure were associated with nephrosclerosis after age-adjustment
- Radiographic and past symptomatic stones were not associated with nephrosclerosis.

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