

# Lessons Learned from CRIC: Chronic Renal Insufficiency Cohort Study

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Illinois Council on Renal Nutrition  
2019 Spring Clinical Meeting



# Who Am I?

## ▷ 2011 – 2014

- Internal Medicine Resident and Chief Resident at Boston Medical Center

## ▷ 2015 – 2018

- Nephrology Fellowship at Johns Hopkins
- Master's of Health Science at Bloomberg School of Public Health

## ▷ 2018 – Present

- Assistant Professor, Division of Nephrology at University of Illinois at Chicago



# Objectives

1. Review the CRIC Study and its purpose.
2. Understand the type of information that is collected from participants during their visits.
3. Explore recent CRIC Study publications in a case-based format.



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# What is CRIC?

- ▷ Ongoing, national, observational, prospective cohort study
- ▷ Established in 2001 by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK) to study the consequences of CKD with a focus on cardiovascular disease and stroke





# Why was there a need for CRIC?

▷ Set out to answer two questions:

- 1) Why does kidney disease get worse in some people, but not in others?**
- 2) Why do persons with kidney disease commonly experience heart disease and stroke?**





# Where is CRIC?

▷ Initially enrolled 2,939 people with moderate CKD across 7 centers in the US

- Chicago, IL
- Ann Arbor, MI
- Philadelphia, PA
- Baltimore, MD
- New Orleans, LA
- Cleveland, OH
- Oakland, CA



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# Who makes up CRIC?

- ▶ Phase 1:
  - 2001 – 2008: recruited ~4,000 individuals
- ▶ Phase 2:
  - 2008 – 2013: allowed for extended follow-up of Phase 1 study participants
- ▶ Phase 3:
  - 2013 – 2015: recruitment of 1,500 new participants with less severe CKD
  - Extended follow-up of Phase 1 and 2 participants
- ▶ Phase 4:
  - Just started recruiting in 2018!





# Phase 1 & 2 Eligibility Criteria:

- ▷ Age: 21 – 74 years old
  
- ▷ Estimated glomerular filtration rate (eGFR):
  - Minimum: 20 mL/min/1.73m<sup>2</sup>
  
  - Maximum eGFR determined by age:
    - Maximum 70 mL/min if aged 21-44y
    - Maximum 60 mL/min if aged 45-64y
    - Maximum 50 mL/min if aged 65-74y





# What did participants do?

- ▷ Participants remain under the care of their usual physicians
- ▷ Informed consent is obtained
- ▷ Weight, height, waist and body water and fat content measured by Bioelectrical Impedance Analysis
- ▷ Blood pressure and heart rate, Ankle brachial index (ABI) in leg & arm
- ▷ EKG 
- ▷ Medical history and recent medication use history
- ▷ Laboratory tests: CBC, metabolic test, liver/kidney/heart function tests, 24h urine sample
- ▷ Questionnaires about quality of life, diet, mood, physical activity
- ▷ Each “baseline visit” takes ~3 hours!





# What about subsequent visits?

- ▷ Participants are contacted by telephone 6 months after Baseline Visit
  - Asked about recent medical events and an updated medication list
  
- ▷ They return annually for various procedures
  - Echocardiograms
  - Coronary calcification measurement
  - eGFR assessment via  $^{131}$ -iothalamate
  - Carotid intima-media thickness
  - Retinal images
  - Ambulatory blood pressures





# Phase 3 & 4 Eligibility Criteria:

- ▷ New objective: enrich the study population by including older participants and participants with preserved kidney function
- ▷ Age: 45 – 79 years of age
- ▷ Estimated glomerular filtration rate (eGFR):
  - Minimum: 45 mL/min/1.73m<sup>2</sup>
  - Included a proteinuria requirement to limit the number of participants who did not experience a decline in renal function

eGFR level, ml/min/1.73m <sup>2</sup>	Urine Dipstick Protein Result	
	Negative/Trace	≥ 1+
45 – 60	25%	75%
61 – 70	0%	100%



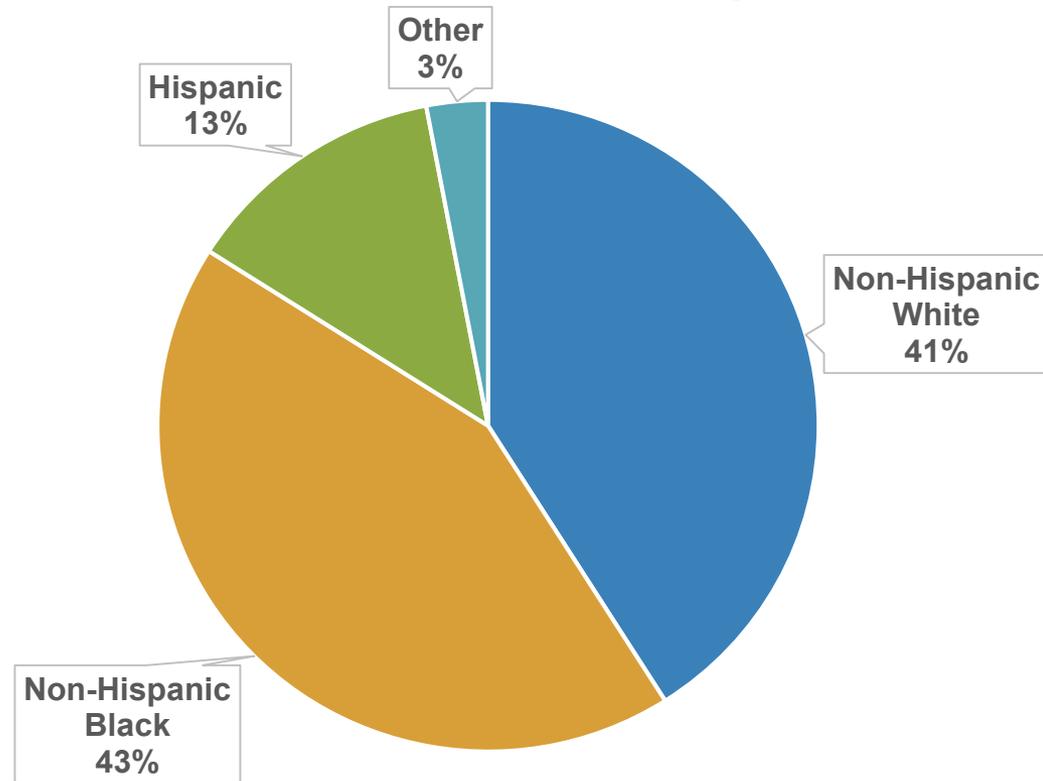
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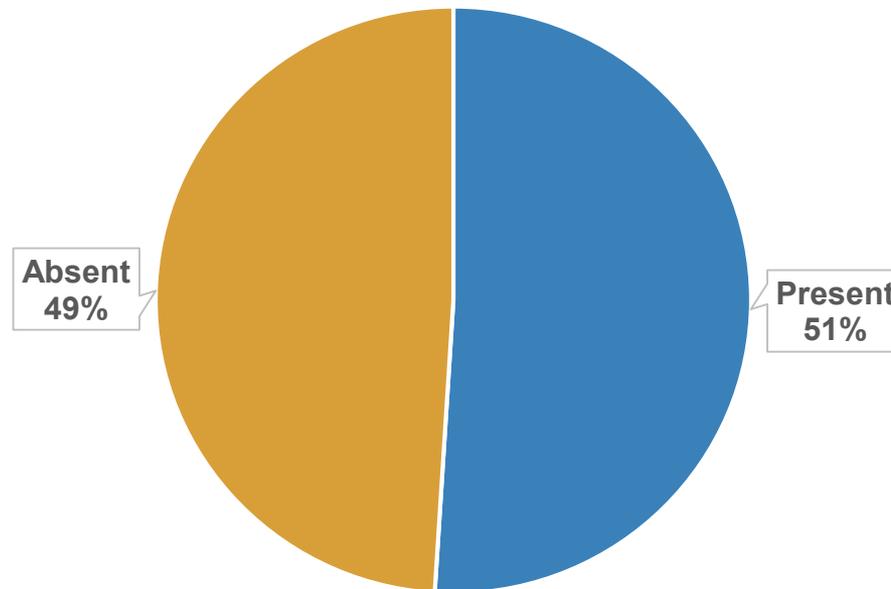
## Race / Ethnicity





# Who makes up CRIC?

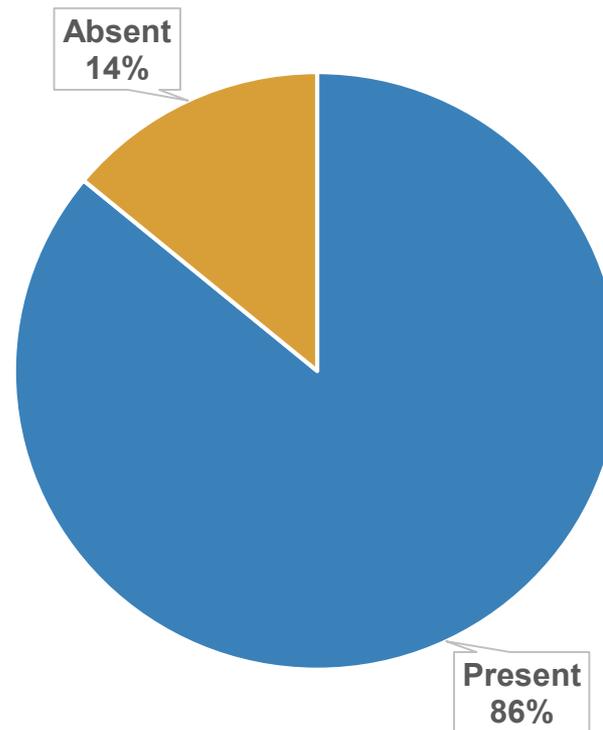
## Diabetes





# Who makes up CRIC?

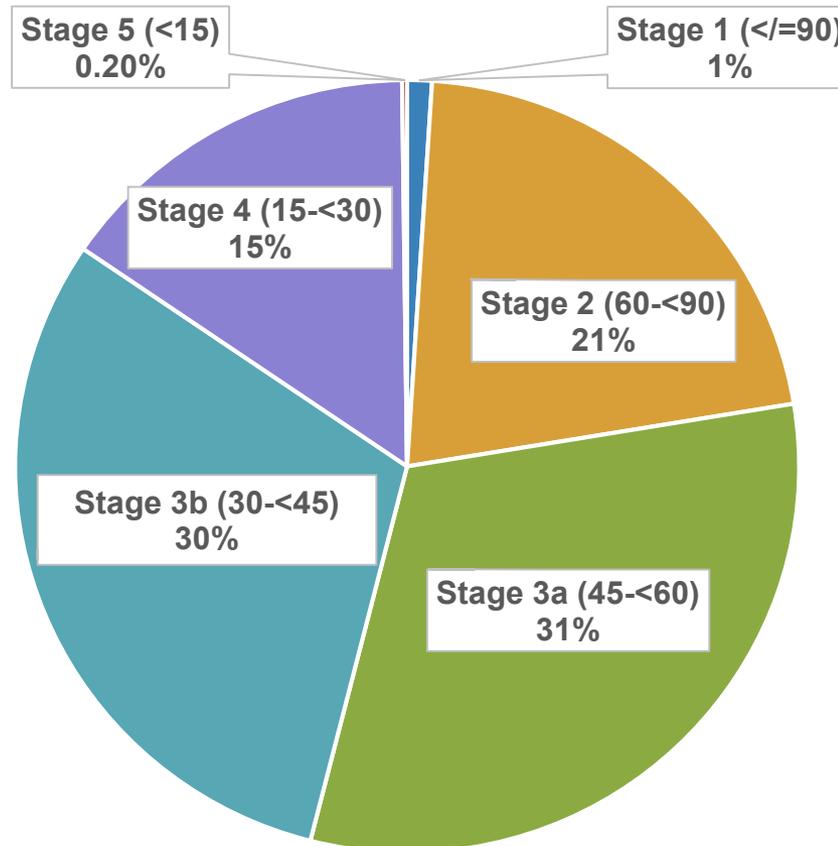
## Hypertension





# Who makes up CRIC?

## Stage of CKD at Baseline Visit



# Major Outcomes of Interest?

## ▷ Cardiovascular Outcomes:

- Myocardial Infarctions
- Stroke
- Peripheral Vascular Disease
- Heart Failure
- Atrial Fibrillation

## ▷ Renal Outcomes:

- Halving of eGFR
- Onset of end-stage renal disease (ESRD)

## ▷ Death:

- All-cause
- Cardiovascular Death

# Objectives

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# Our first case...

- ▷ A 58yo man with a history of Stage 3a CKD (eGFR ~ 48 mL/min) and hypertension presents to renal clinic for follow-up.
- ▷ He reports the following:
  - Currently smokes ½ pack of cigarettes per day
  - Drinks 1-2 alcoholic beverages every night after work
  - Previously regularly used illicit substances (cocaine and heroin) but has “been clean” for the past six months
- ▷ He is wondering if his substance use affects his kidney function. What do you tell him? (more than one answer is correct)
  - a) Smoking ½ ppd won't worsen his CKD, but he should still try to cut down.
  - b) Drinking alcohol in moderation is okay and may even be beneficial for his health!
  - c) Heroin decreases kidney function over time but cocaine doesn't. He should abstain from both.
  - d) He should stop smoking marijuana as this certainly worsens kidney function.





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# Self-Reported Tobacco, Alcohol, and Illicit Drug Use and Progression of Chronic Kidney Disease

Joshua D. Bundy <sup>1</sup>, and the CRIC Study Investigators

*Clin J Am Soc Nephrol* 13: ●●●–●●●, 2018. doi: <https://doi.org/10.2215/CJN.11121017>

<sup>1</sup>Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, Louisiana; <sup>2</sup>

- ▷ 3,939 CRIC participants
- ▷ Asked about tobacco smoking, alcohol drinking, marijuana use, and hard illicit drugs (cocaine, heroin, methamphetamine) at baseline and follow-up visits
- ▷ Primary outcome:
  - Development of ESRD or halving of eGFR
- ▷ Secondary outcome:
  - Mortality



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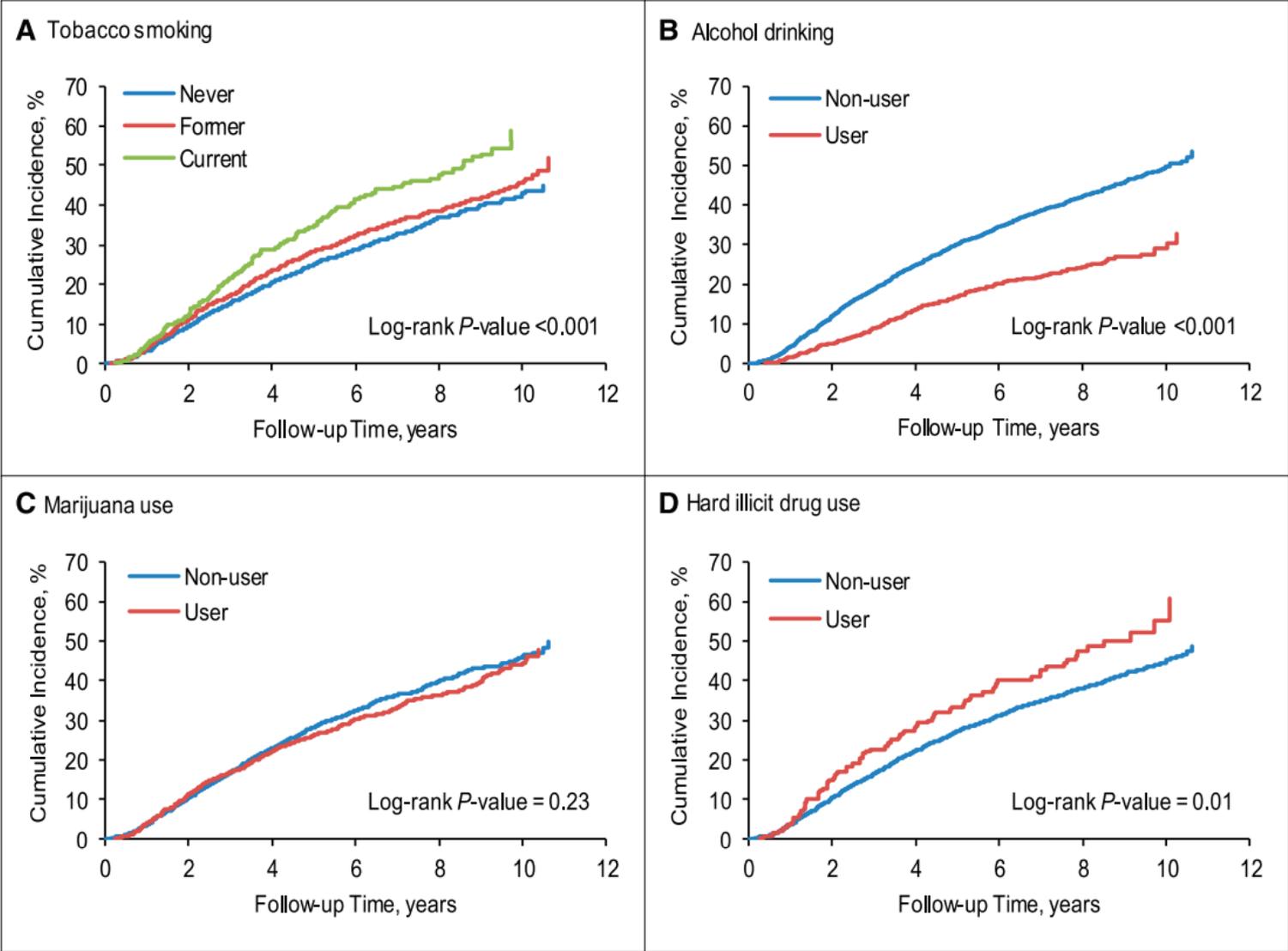
- ▷ **On average...**
- ▷ Age = 58yo
- ▷ Women = 45%
- ▷ Followed for ~5.5 years
- ▷ Current tobacco smoking at baseline = 13%
- ▷ Current alcohol drinking = 20%
- ▷ Current marijuana use = 33%
- ▷ Current hard illicit drug use = 12%

These responses were updated annually



# Self-Reported Tobacco, Alcohol, and Illicit Drug Use and Progression of Chronic Kidney Disease

Figure 1. Cumulative incidence of CKD progression



**Table 2. Hazard ratios and 95% confidence intervals of CKD progression and all-cause mortality according to cumulative average tobacco smoking, alcohol drinking, marijuana use, and hard illicit drug use among 3939 patients with CKD**

Variable	Univariable		Age, Sex, Race/Ethnicity, and Clinical Site Adjusted		Multivariable Adjusted	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
<b>CKD progression</b>						
Tobacco smoking	1.52 (1.30 to 1.79)	<0.001	1.25 (1.06 to 1.48)	<0.01	1.02 (0.86 to 1.21)	0.83
Alcohol drinking	0.50 (0.42 to 0.59)	<0.001	0.63 (0.53 to 0.76)	<0.001	1.06 (0.88 to 1.29)	0.54
Marijuana use	0.93 (0.83 to 1.05)	0.23	0.92 (0.81 to 1.04)	0.17	0.94 (0.82 to 1.07)	0.35
Hard illicit drug use	1.26 (1.02 to 1.56)	0.03	1.25 (1.01 to 1.56)	0.04	1.25 (1.00 to 1.55)	0.05
<i>Cocaine use</i>	1.16 (0.83 to 1.63)	0.37	1.00 (0.71 to 1.41)	0.99	1.28 (0.90 to 1.83)	0.17
<i>Heroin use</i>	2.44 (1.70 to 3.50)	<0.001	1.77 (1.23 to 2.56)	0.002	1.57 (1.08 to 2.29)	0.02
<i>Methamphetamine use</i>	1.04 (0.78 to 1.39)	0.77	1.26 (0.94 to 1.68)	0.12	1.09 (0.81 to 1.47)	0.55
<b>All-cause mortality</b>						
Tobacco smoking	1.87 (1.58 to 2.22)	<0.001	1.95 (1.64 to 2.33)	<0.001	1.86 (1.54 to 2.24)	<0.001
Alcohol drinking	0.50 (0.41 to 0.62)	<0.001	0.58 (0.47 to 0.72)	<0.001	0.73 (0.58 to 0.91)	<0.01
Marijuana use	0.81 (0.71 to 0.93)	0.003	1.10 (0.95 to 1.28)	0.19	1.11 (0.96 to 1.30)	0.16
Hard illicit drug use	1.30 (1.03 to 1.65)	0.03	1.70 (1.33 to 2.16)	<0.001	1.41 (1.10 to 1.81)	<0.01
<i>Cocaine use</i>	1.49 (1.03 to 2.16)	0.04	2.21 (1.52 to 3.22)	<0.001	2.17 (1.46 to 3.22)	<0.001
<i>Heroin use</i>	2.16 (1.47 to 3.20)	<0.001	2.05 (1.38 to 3.06)	<0.001	1.40 (0.93 to 2.10)	0.10
<i>Methamphetamine use</i>	1.01 (0.73 to 1.40)	0.94	1.37 (0.99 to 1.91)	0.06	1.21 (0.87 to 1.70)	0.25

HRs compare persistent tobacco smoking throughout follow-up with nonsmoking, persistent alcohol drinking throughout follow-up with nondrinking, persistent marijuana use throughout follow-up with no marijuana use, and persistent hard illicit drug use (use of cocaine, heroin, or methamphetamine) throughout follow-up with no hard illicit drug use. Multivariable-adjusted analyses are adjusted for age, sex, race/ethnicity, clinical site, education, eGFR, proteinuria, history of diabetes, body mass index, systolic BP, hemoglobin, use of nonsteroidal anti-inflammatory drugs, and current smoking. HR, hazard ratio; 95% CI, 95% confidence interval.



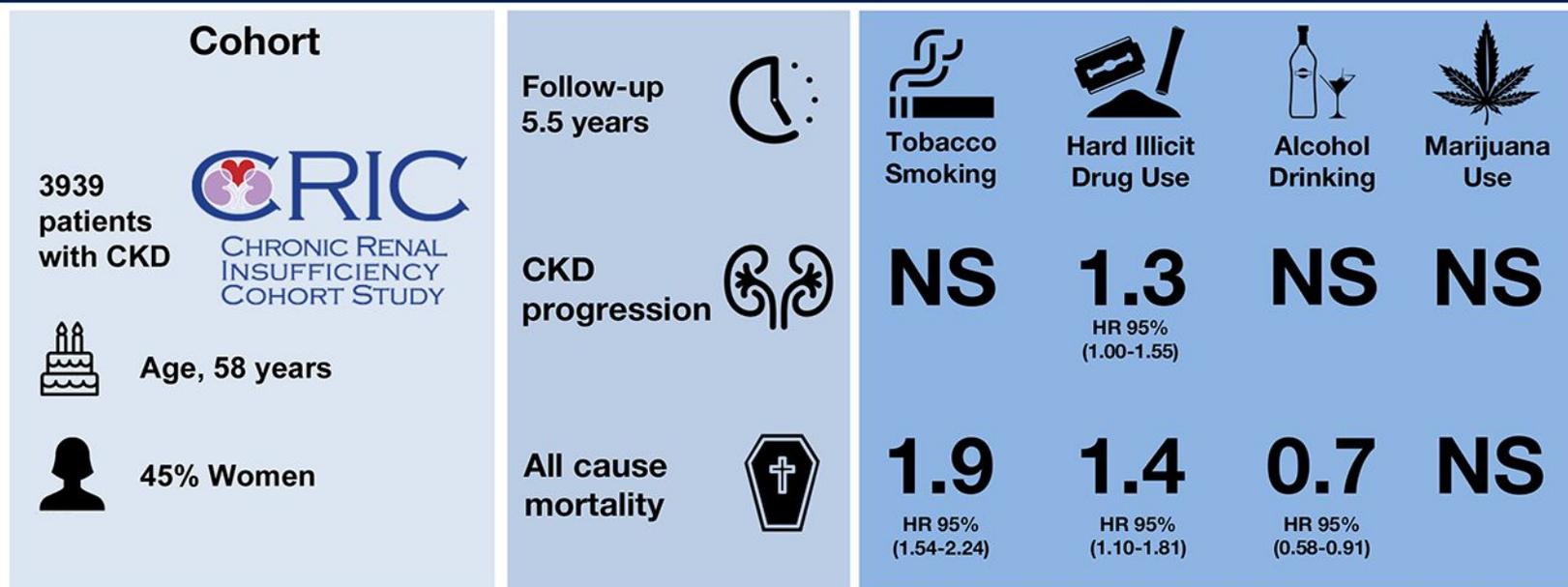
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# Is tobacco smoking, alcohol drinking and illicit drug use associated with CKD progression and mortality?



**Conclusions** Hard illicit drug use is associated with higher all-cause mortality and CKD progression while weekly alcohol drinking is associated with lower all-cause mortality among CKD patients.

Joshua Bundy, Lydia Bazzano, Dawei Xie, Janet Cohan, Jacqueline Dolata, Jeffrey Fink, Chi-yuan Hsu, Kenneth Jamerson, James Lash, Gail Makos, Susan Steigerwalt, Xue Wang, Katherine Mills, Jing Chen, and Jiang He. **Self-reported Tobacco, Alcohol, and Illicit Drug Use and Progression of Chronic Kidney Disease.** CJASN doi: 10.2215/CJN.11121017.

Joshua D. Bundy et al. CJASN doi:10.2215/CJN.11121017



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  - d) He should stop smoking marijuana as this certainly worsens kidney function.



# Your next patient is...

- ▷ A 69yo woman with a history of Stage 3b CKD (eGFR ~ 32 mL/min) due to hypertension presents to renal clinic for follow-up.
- ▷ Physical exam is notable for a BP of 180/104 and 2+ pitting edema in her lower extremities.
- ▷ You've spent many prior clinic sessions educating her about a low sodium diet but to no avail!





# Your next patient is...

- ▷ She asks you what exactly is the big deal with consuming too much salt? How does it affect her health anyway? Is there a way to check to see how much she is consuming?
  - a) Excess salt intake leads to water retention and brain swelling and increases her risk of stroke!
  - b) In people with CKD, excess salt intake has been linked to excess cardiovascular events (CHF, stroke, etc.).
  - c) There is no way to quantify whether she is decreasing her salt intake. Reporting what she eats is the best way to get an idea if her diet is “low enough in salt.”





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# Sodium Excretion and the Risk of Cardiovascular Disease in Patients With Chronic Kidney Disease



Katherine T. Mills, PhD; Jing Chen, MD; Wei Yang, PhD; Lawrence J. Appel, MD; John W. Kusek, PhD; Arnold Alper, MD; Patrice Delafontaine, M  
Martin G. Keane, MD; Emile Mohler, MD; Akinlolu Ojo, MD, PhD; Mahboob Rahman, MD; Ana C. Ricardo, MD; Elsayed Z. Soliman, MD;  
Susan Steigerwalt, MD; Raymond Townsend, MD; Jiang He, MD, PhD; for the Chronic Renal Insufficiency Cohort (CRIC) Study Investigators

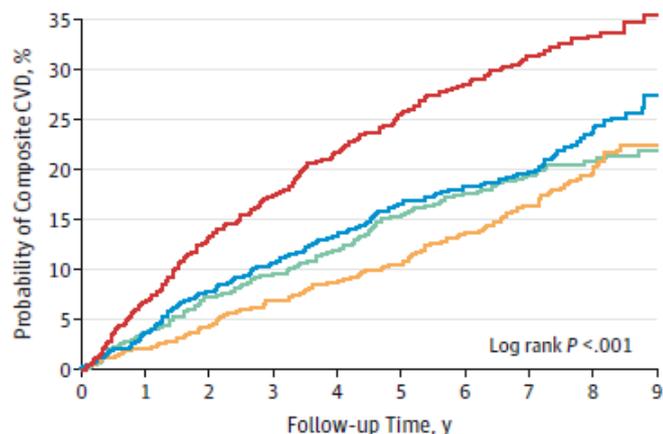
JAMA. 2016;315(20):2200-2210. doi:10.1001/jama.2016.4447

- ▷ 3,757 CRIC participants
- ▷ Underwent three 24-hour urinary sodium measurements (calibrated to sex-specific mean 24-hour urinary creatinine measurements)
- ▷ Sodium measurements were divided into quartiles
  - Lowest → <2,897 mg/24 hours
  - Highest → 4,548 mg/24 hours
- ▷ Followed for ~6.8 years
- ▷ Main Outcomes:
  - Congestive Heart Failure
  - Myocardial Infarction
  - Stroke
  - “Composite of CVD Events”



Figure 1. Cumulative Kaplan-Meier Estimates of Cardiovascular Diseases According to Quartile of Calibrated 24-Hour Urinary Sodium Excretion

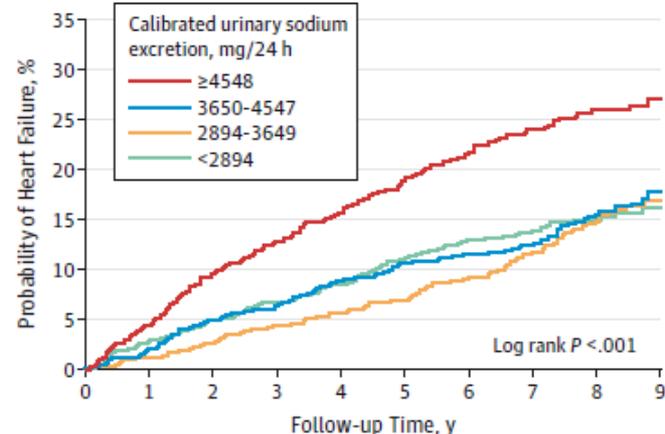
**A** Composite CVD events



No. at risk

Calibrated urinary sodium excretion, mg/24 h	0	1	2	3	4	5	6	7	8	9
≥4548	937	752	617	480	215					
3650-4547	930	824	720	593	277					
2894-3649	926	850	752	637	290					
<2894	943	821	730	594	291					

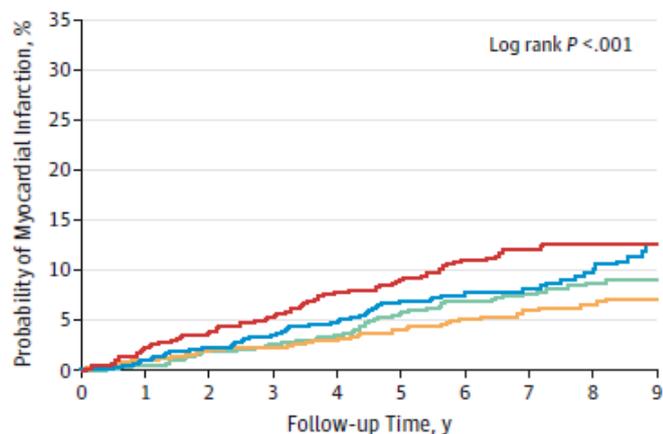
**B** Congestive heart failure



No. at risk

Calibrated urinary sodium excretion, mg/24 h	0	1	2	3	4	5	6	7	8	9
≥4548	935	778	658	510	232					
3650-4547	933	847	751	635	303					
2894-3649	935	873	787	673	311					
<2894	938	834	749	618	307					

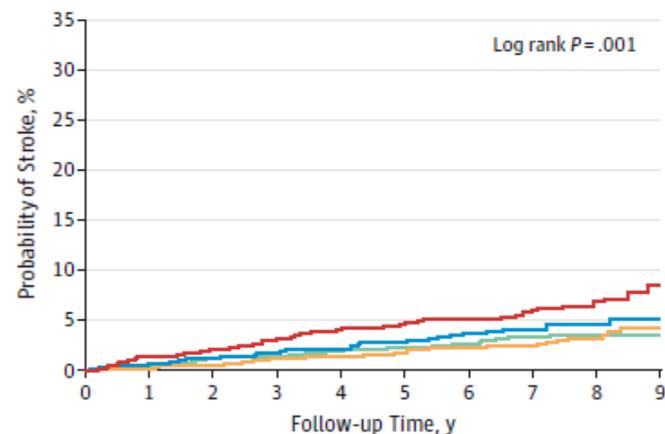
**C** Myocardial infarction



No. at risk

Calibrated urinary sodium excretion, mg/24 h	0	1	2	3	4	5	6	7	8	9
≥4548	938	823	700	551	257					
3650-4547	936	872	783	652	316					
2894-3649	935	878	803	694	326					
<2894	942	862	790	655	319					

**D** Stroke



No. at risk

Calibrated urinary sodium excretion, mg/24 h	0	1	2	3	4	5	6	7	8	9
≥4548	940	843	732	575	262					
3650-4547	935	882	804	680	340					
2894-3649	939	893	821	717	338					
<2894	939	865	800	678	339					



**Table 2. Composite Cardiovascular Disease, Congestive Heart Failure, Myocardial Infarction, and Stroke According to Quartile of Calibrated 24-Hour Urinary Sodium Excretion**

Variable	No. of Participants	Calibrated Urinary Sodium Excretion, mg/24 h <sup>a</sup>				P Value for Trend
		<2894	2894-3649	3650-4547	≥4548	
No. of participants		939	940	939	939	
<b>Composite CVD<sup>b</sup></b>						
Events		174	159	198	273	
Person-years		5804	5972	5739	5012	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		18.4 (15.8-20.9)	16.5 (14.1-18.8)	20.6 (18.0-23.1)	29.8 (26.7-32.7)	<.001
Model 1, HR (95% CI) <sup>d</sup>	3736	1 [Reference]	0.88 (0.71-1.10)	1.14 (0.93-1.41)	1.79 (1.46-2.19)	<.001
P value			.27	.22	<.001	
Model 2, HR (95% CI)	3528	1 [Reference]	0.85 (0.68-1.07)	0.99 (0.80-1.24)	1.31 (1.05-1.63)	.002
P value			.17	.96	.02	
Model 3, HR (95% CI)	3528	1 [Reference]	0.87 (0.69-1.10)	1.01 (0.81-1.26)	1.36 (1.09-1.70)	<.001
P value			.24	.96	.007	
<b>Congestive Heart Failure</b>						
Events		125	117	127	206	
Person-years		5938	6216	5998	5235	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		13.3 (11.0-15.5)	12.0 (9.9-14.0)	13.3 (11.1-15.4)	23.2 (20.3-26.0)	<.001
Model 1, HR (95% CI) <sup>d</sup>	3741	1 [Reference]	0.90 (0.70-1.16)	1.01 (0.78-1.30)	1.90 (1.50-2.41)	<.001
P value			.41	.96	<.001	
Model 2, HR (95% CI)	3533	1 [Reference]	0.86 (0.66-1.13)	0.83 (0.63-1.08)	1.27 (0.98-1.65)	.02
P value			.27	.16	.08	
Model 3, HR (95% CI)	3533	1 [Reference]	0.89 (0.68-1.17)	0.84 (0.65-1.11)	1.34 (1.03-1.74)	.008
P value			.40	.22	.03	

<sup>d</sup>Model 1: adjusted for age, sex, race, and clinic site. Model 2: model 1 plus education; waist circumference; lean body mass index; body mass index; cigarette smoking; alcohol drinking; physical activity; low-density lipoprotein cholesterol; glucose; history of CVD; use of antidiabetic medications, lipid-lowering medications, diuretics, renin-angiotensin system blocking agents, and other antihypertensive medications; and urinary creatinine excretion. Model 3: model 2 plus adjustment for baseline estimated glomerular filtration rate.



**Table 2. Composite Cardiovascular Disease, Congestive Heart Failure, Myocardial Infarction, and Stroke According to Quartile of Calibrated 24-Hour Urinary Sodium Excretion**

Variable	No. of Participants	Calibrated Urinary Sodium Excretion, mg/24 h <sup>a</sup>				P Value for Trend
		<2894	2894-3649	3650-4547	≥4548	
No. of participants		939	940	939	939	
<b>Myocardial Infarction</b>						
Events		69	54	83	99	
Person-years		6195	6336	6175	5569	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		7.8 (6.0-9.7)	5.8 (4.3-7.3)	8.6 (6.8-10.3)	10.9 (8.7-12.9)	.002
Model 1, HR (95% CI) <sup>d</sup>	3751	1 [Reference]	0.73 (0.51-1.04)	1.10 (0.79-1.53)	1.42 (1.02-1.98)	.002
P value			.08	.57	.04	
Model 2, HR (95% CI)	3540	1 [Reference]	0.66 (0.44-0.97)	1.00 (0.70-1.43)	1.12 (0.77-1.62)	.14
P value			.03	.99	.56	
Model 3, HR (95% CI)	3540	1 [Reference]	0.66 (0.45-0.97)	1.00 (0.70-1.43)	1.15 (0.79-1.66)	.11
P value			.04	.99	.46	
<b>Stroke</b>						
Events		28	28	39	53	
Person-years		6293	6479	6337	5719	
Cumulative incidence at median 6.8 y follow-up, % (95% CI) <sup>c</sup>		2.7 (1.6-3.7)	2.8 (1.7-3.8)	4.1 (2.8-5.3)	6.4 (4.6-8.1)	<.001
Model 1, HR (95% CI) <sup>d</sup>	3753	1 [Reference]	1.04 (0.61-1.77)	1.55 (0.94-2.54)	2.51 (1.55-4.07)	<.001
P value			.88	.09	<.001	
Model 2, HR (95% CI)	3542	1 [Reference]	0.92 (0.53-1.59)	1.38 (0.83-2.29)	1.80 (1.08-3.00)	.007
P value			.76	.21	.02	
Model 3, HR (95% CI)	3542	1 [Reference]	0.93 (0.54-1.61)	1.38 (0.83-2.29)	1.81 (1.08-3.02)	.006
P value			.79	.21	.02	

<sup>d</sup>Model 1: adjusted for age, sex, race, and clinic site. Model 2: model 1 plus education; waist circumference; lean body mass index; body mass index; cigarette smoking; alcohol drinking; physical activity; low-density lipoprotein cholesterol; glucose; history of CVD; use of antidiabetic medications, lipid-lowering medications, diuretics, renin-angiotensin system blocking agents, and other antihypertensive medications; and urinary creatinine excretion. Model 3: model 2 plus adjustment for baseline estimated glomerular filtration rate.





# Your next patient is...

- ▷ She asks you what exactly is the big deal with consuming too much salt? How does it affect her health anyway? Is there a way to check to see how much she is consuming?
  - a) Excess salt intake leads to water retention and brain swelling and increases her risk of stroke!
  - b) **In people with CKD, excess salt intake has been linked to excess cardiovascular events(CHF,stroke, etc.).**
  - c) There is no way to quantify whether she is decreasing her salt intake. Reporting what she eats is the best way to get an idea if her diet is “low enough in salt.”





# Your next patient is...

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  - b) **In people with CKD, excess salt intake has been linked to excess cardiovascular events(CHF,stroke, etc.).**
  - c) ~~There is no way to quantify whether she is decreasing her salt intake. Reporting what she eats is the best way to get an idea if her diet is “low enough in salt.”~~

Consider quantifying  
24h urine sodium levels  
in CKD patients?



# Your last patient isn't satisfied...

- ▷ She wants to know if consuming less salt will slow her kidney disease.



- ▷ What do you tell her?
  - a) It will certainly slow her CKD progression
  - b) It might slow her CKD progression, but “we” don't know this yet.

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# Urinary Sodium Is a Potent Correlate of Proteinuria: Lessons from the Chronic Renal Insufficiency Cohort Study

Received: May 30, 2012

Accepted: August 26, 2012

Published online: October 12, 2012

- ▷ They used the same 24-hour urine sodium measurements
- ▷ Also looked at 24-hour urine protein measurements
- ▷ Objective:
  - Determine the relationship between urinary sodium and protein excretion in patients with CKD



# Urinary Sodium Is a Potent Correlate of Proteinuria: Lessons from the Chronic Renal Insufficiency Cohort Study

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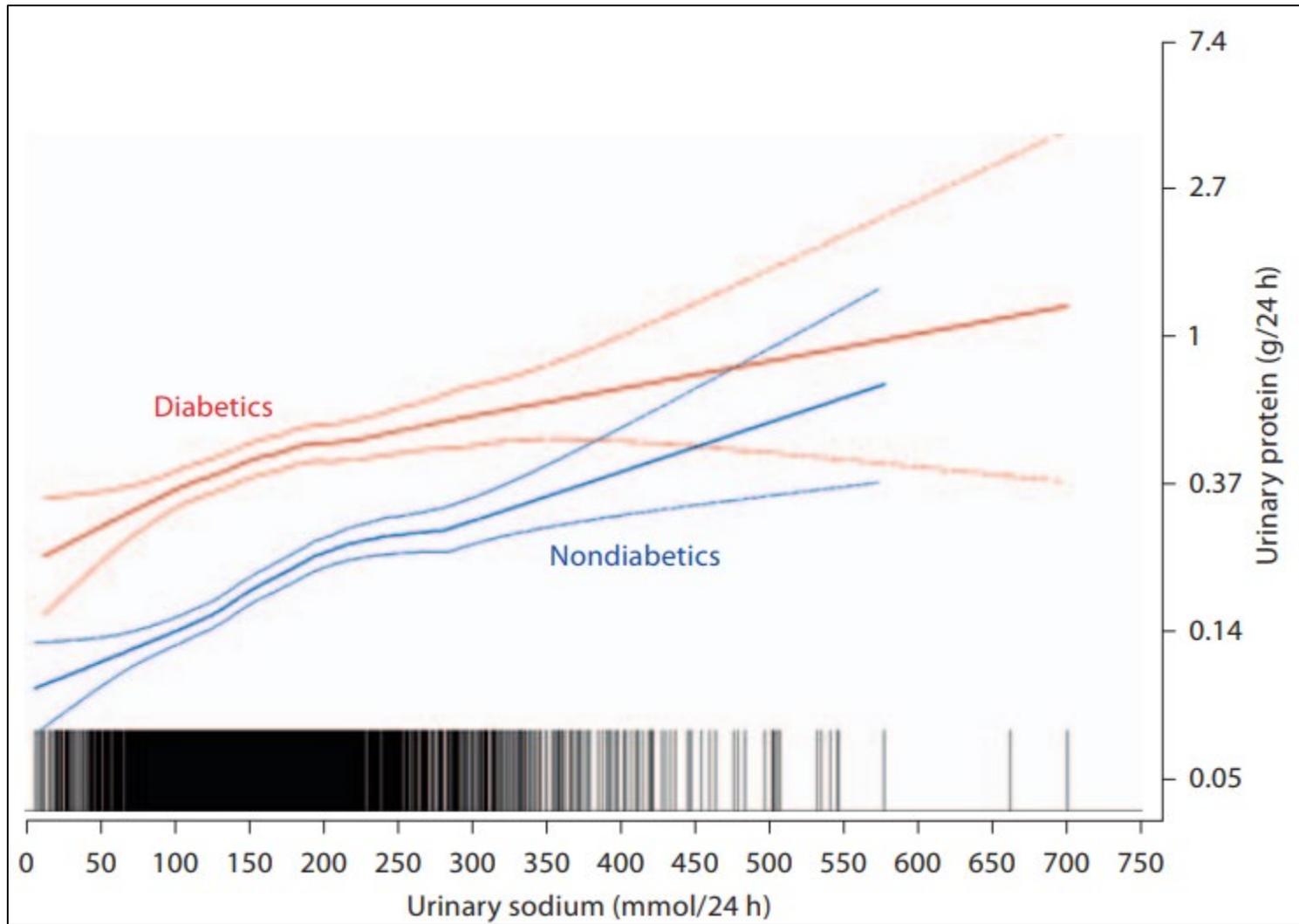
Published online: October 12, 2012

- ▷ N = 3,673 participants (mean age 58 years old)
- ▷ Baseline characteristics were very similar to the previous study
- ▷ Diabetics = 1,766 participants
- ▷ Nondiabetics = 1,907 participants



## Figure 1.

24-hour urinary protein excretion in relation to 24-hour urinary sodium excretion in diabetics and nondiabetics



Vertical lines at the bottom of the figure indicate the numbers of patients.



# Your patient is finally satisfied...



- ▷ What do you tell her?
  - a) It will certainly slow her CKD progression
  - b) **It might slow her CKD progression, but “we” don’t know this yet.**

# Your next patient wants to know...

- ▷ How does becoming a vegetarian impact her CKD?
- She is 58 years old and recently progressed from Stage 3a CKD to 3b CKD. Her GFR is 43 mL/min.
  - What do you tell her?
- a) Eliminating animal sources of protein increases her risk for protein energy malnutrition, a risk factor for death in patients with CKD.
- b) Plant proteins may be preferred in CKD because of lower acid loads.
- c) Diet has no impact on her CKD progression.



# Your next patient wants to know...

- ▷ How does becoming a vegetarian impact her CKD?
- She is 58 years old and recently progressed from Stage 3a CKD to 3b CKD. Her GFR is 44 mL/min.
  - What do you tell her?
- a) **Eliminating animal sources of protein increases her risk for protein energy malnutrition, a risk factor for death in patients with CKD.**
- b) **Plant proteins may be preferred in CKD because of lower acid loads.**
- c) Diet has no impact on her CKD progression.



# Plant Protein Intake is Associated With Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients With Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

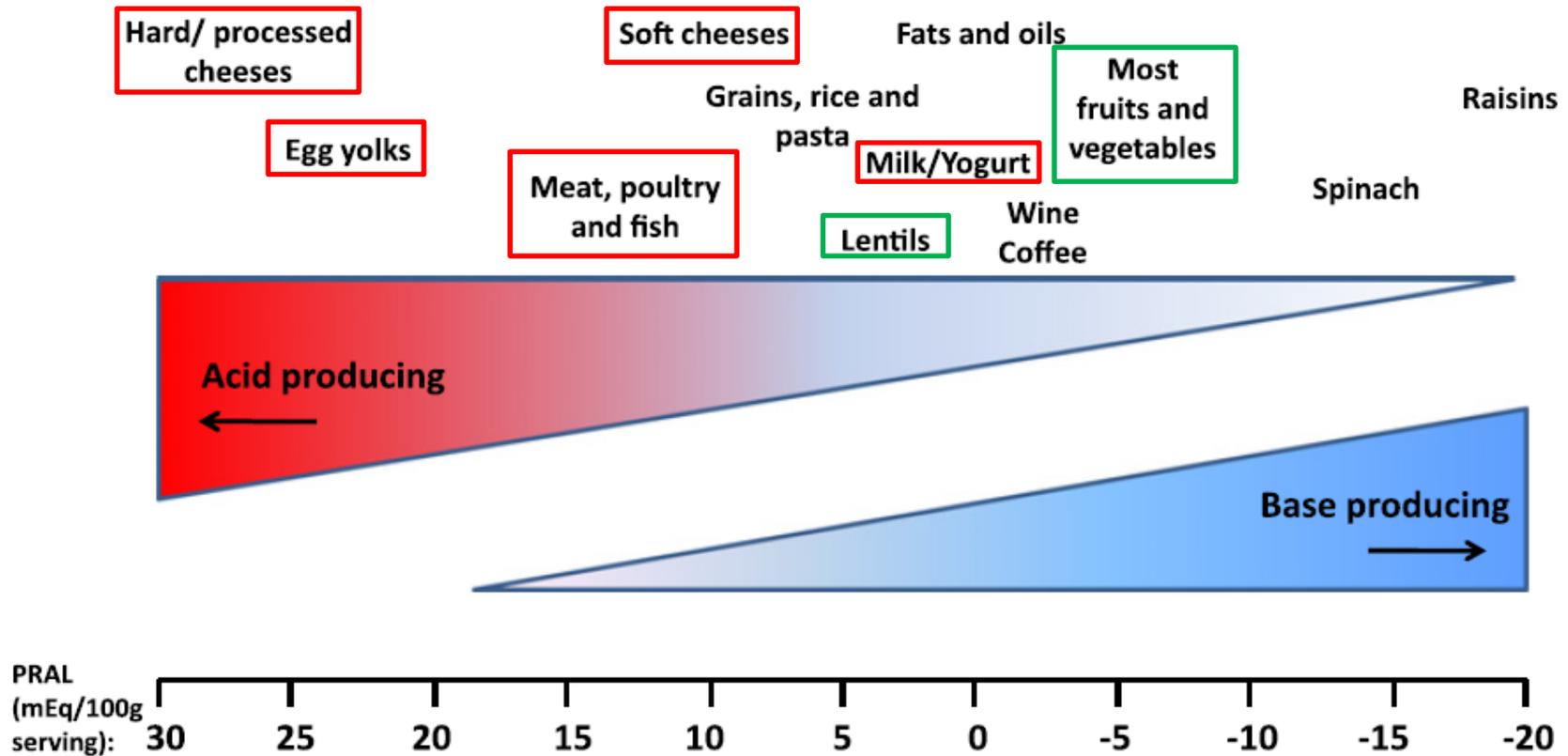
Julia J. Scialla, MD, MHS

*Journal of Renal Nutrition*, Vol 22, No 4 (July), 2012: pp 379-388

- ▷ Plant proteins, compared to animal proteins, may be preferred in CKD for 2 reasons:
  - 1) They have a lower bioavailability of phosphate
  - 2) They provide a lower acid load



# Animal Protein versus Plant Protein



# Plant Protein Intake is Associated With Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients With Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

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- ▶ Study sample: 2,938 CRIC participants who completed a Diet History Questionnaire
- ▶ Predictors:
  - Percentage of total protein intake from plant sources
- ▶ Outcomes:
  - Serum phosphate
  - Serum bicarbonate
  - Plasma fibroblast growth factor-23 (FGF-23)
  - PTH
  - Hemoglobin



# Plant Protein Intake is Associated With Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients With Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

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- ▷ Predictors:
  - Percentage of total protein intake from plant sources
- ▷ Outcomes:
  - Serum phosphate
  - Serum bicarbonate
  - FGF-23
  - PTH
  - Hemoglobin

FGF-23 is a hormone that maintains phosphate homeostasis as eGFR decreases.

FGF-23 levels rise earlier in CKD than phosphate.

Is thought to be a more sensitive biomarker for abnormal phosphate metabolism



# How was % plant protein consumption calculated?

- ▶ National Cancer Institute Diet History Questionnaire (DHQ)
  - Asks about 124 food items consumed over the past 12 months (portion size and frequency)
  - 36 pages long!
- ▶ Percentage of animal protein in 255 foods from the DHQ were estimated
- ▶ Percentage of animal protein in the food item was multiplied by the total protein content of the food (in grams) to determine the **total animal protein content** in grams
- ▶ The remaining protein was assigned as the **total plant protein content**

1. **Over the past 12 months, how often did you drink tomato juice or vegetable juice?**

- NEVER (Go To Question 2)
- 1 time per month or less       1 time per day
- 2-3 times per month             2-3 times per day
- 1-2 times per week             4-5 times per day
- 3-4 times per week             6 or more times per day
- 5-6 times per week

**1a. Each time you drank tomato juice or vegetable juice, how much did you usually drink?**

- Less than 3/4 cup (6 ounces)
- 3/4 to 1-1/4 cups (6 to 10 ounces)
- More than 1-1/4 cups (10 ounces)

2. **Over the past 12 months, how often did you drink orange juice or grapefruit juice?**

- NEVER (Go To Question 3)
- 1 time per month or less       1 time per day
- 2-3 times per month             2-3 times per day
- 1-2 times per week             4-5 times per day
- 3-4 times per week             6 or more times per day
- 5-6 times per week

**2a. Each time you drank orange juice or grapefruit juice, how much did you usually drink?**

**Over the past 12 months...**

4. **How often did you drink other fruit drinks (e.g. cranberry cocktail, Hi-C, lemonade, or Kool-Aid, diet or regular)?**

- NEVER (Go To Question 5)
- 1 time per month or less       1 time per day
- 2-3 times per month             2-3 times per day
- 1-2 times per week             4-5 times per day
- 3-4 times per week             6 or more times per day
- 5-6 times per week

**4a. Each time you drank fruit drinks, how much did you usually drink?**

- Less than 1 cup (8 ounces)
- 1 to 2 cups (8 to 16 ounces)
- More than 2 cups (16 ounces)

**4b. How often were your fruit drinks diet or sugar-free drinks?**

- Almost never or never
- About 1/4 of the time
- About 1/2 of the time
- About 3/4 of the time
- Almost always or always

5. **How often did you drink milk as a beverage (NOT in coffee, NOT in cereal)? (Please include chocolate milk and hot chocolate)**

Over the past 12 months...

**67. How often did you eat turkey or chicken COLD CUTS (such as loaf, luncheon meat, turkey ham, turkey salami, or turkey pastrami)? (We will ask about other turkey or chicken later.)**

- NEVER (Go To Question 68)
- 1-6 times per year                       2 times per week
- 7-11 times per year                       3-4 times per week
- 1 time per month                         5-6 times per week
- 2-3 times per month                       1 time per day
- 1 time per week                          2 or more times per day

**67a. Each time you ate turkey or chicken COLD CUTS, how much did you usually eat?**

- Less than 1 slice
- 1 to 3 slices
- More than 3 slices



**68. How often did you eat luncheon or deli-style ham? (We will ask about other ham later.)**

**69. How often did you eat other cold cuts or luncheon meats (such as bologna, salami, corned beef, pastrami, or others, including low-fat)? (Please do not include ham, turkey, or chicken cold cuts.)**

- NEVER (Go To Question 70)
- 1-6 times per year                       2 times per week
- 7-11 times per year                       3-4 times per week
- 1 time per month                         5-6 times per week
- 2-3 times per month                       1 time per day
- 1 time per week                          2 or more times per day

**69a. Each time you ate other cold cuts or luncheon meats, how many did you usually eat?**

- Less than 1 slice
- 1 to 3 slices
- More than 3 slices

**69b. How often were the other cold cuts or luncheon meats you ate light, low-fat, or fat-free? (Please do not include ham, turkey, or chicken cold cuts.)**

- Almost never or never
- About 1/4 of the time
- About 1/2 of the time
- About 3/4 of the time
- Almost always or always

**70. How often did you eat canned tuna (including in salads, sandwiches, or casseroles)?**

Over the past 12 months...

**97a. Each time you ate potato chips, tortilla chips, or corn chips, how much did you usually eat?**

- Less than 10 chips or less than 1 cup
- 10 to 25 chips or 1 to 2 cups
- More than 25 chips or more than 2 cups

**97b. How often were the chips you ate Wow chips or other chips made with fat substitute (Olean or Olestra)?**

- Almost never or never
- About 1/4 of the time
- About 1/2 of the time
- About 3/4 of the time
- Almost always or always

**97c. How often were the chips you ate other low-fat or fat-free chips?**

- Almost never or never
- About 1/4 of the time
- About 1/2 of the time
- About 3/4 of the time
- Almost always or always

**98. How often did you eat popcorn (including low-fat)?**

- NEVER (Go To Question 99)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2 times per week
- 3-4 times per week
- 5-6 times per week

**99a. Each time you ate pretzels, how many did you usually eat?**

- Less than 5 average twists
- 5 to 20 average twists
- More than 20 average twists

**100. How often did you eat peanuts, walnuts, seeds, or other nuts?**

- NEVER (Go To Question 101)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

**100a. Each time you ate peanuts, walnuts, seeds, or other nuts, how much did you usually eat?**

- Less than 1/4 cup
- 1/4 to 1/2 cup
- More than 1/2 cup

**101. How often did you eat energy, high protien, or breakfast bars such as Power Bars, Balance, Clif, or others?**

- NEVER (Go To Question 102)
- 1-6 times per year
- 7-11 times per year
- 1 time per month
- 2-3 times per month
- 1 time per week
- 2 times per week
- 3-4 times per week
- 5-6 times per week
- 1 time per day
- 2 or more times per day

# Plant Protein Intake is Associated With Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients With Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

Julia J. Scialla, MD, MHS

*Journal of Renal Nutrition*, Vol 22, No 4 (July), 2012: pp 379-388

- ▷ **Results:**
- ▷ Median protein intake from animal sources: 41.8g/d
- ▷ Median protein intake from plant sources: 20.7 g/d



# Plant Protein Intake is Associated With Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients With Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

**Table 1.** Characteristics of Study Population Stratified by Quintiles of Percentage of Total Protein Intake From Plant Sources (n = 2,938)

Characteristic Mean ± SD or n (%)	Quintiles of Percentage of Protein Intake from Plant Sources					P
	1 <24% (n = 587)	2 24%-29% (n = 588)	3 30%-35% (n = 588)	4 36%-44% (n = 587)	5 >44% (n = 588)	
<b>Demographics</b>						
Age (years)	56.5 ± 11.3	57.8 ± 11.1	58.5 ± 11.3	59.5 ± 9.9	59.6 ± 10.9	<.001
Female sex	232 (39.5%)	272 (46.3%)	263 (44.7%)	302 (51.4%)	321 (54.6%)	<.001
Race/ethnicity						<.001
Non-Hispanic white	279 (47.5%)	313 (53.2%)	309 (52.6%)	293 (49.9%)	254 (43.2%)	
Non-Hispanic black	257 (43.8%)	248 (42.2%)	228 (38.8%)	248 (42.2%)	249 (42.3%)	
Hispanic	39 (6.6%)	17 (2.9%)	27 (4.6%)	22 (3.7%)	30 (5.1%)	
Other	12 (2.0%)	10 (1.7%)	24 (4.1%)	24 (4.1%)	55 (9.4%)	
Income*						.02
\$20,000 or less	152 (25.9%)	148 (25.2%)	137 (23.3%)	149 (25.4%)	173 (29.4%)	
\$20,001-\$50,000	146 (24.9%)	152 (25.9%)	145 (24.7%)	144 (24.5%)	152 (25.9%)	
\$50,000-\$100,000	124 (21.1%)	117 (19.9%)	144 (24.5%)	137 (23.3%)	105 (17.9%)	
>\$100,000	84 (14.3%)	86 (14.6%)	60 (10.2%)	67 (11.4%)	53 (9.0%)	
<b>Clinical characteristics</b>						
Diabetes	278 (47.4%)	271 (46.1%)	261 (44.4%)	267 (45.5%)	236 (40.1%)	.12
Cardiovascular disease	199 (33.9%)	188 (32.0%)	184 (31.3%)	202 (34.4%)	189 (32.1%)	.75
Hypertension	516 (87.9%)	505 (85.9%)	494 (84.0%)	494 (84.2%)	491 (83.5%)	.19
Body mass index (kg/m <sup>2</sup> )	33.2 ± 8.0	32.8 ± 8.2	31.8 ± 7.3	31.9 ± 7.7	30.0 ± 7.3	<.001
Estimated GFR (mL/ minute/1.73 m <sup>2</sup> )	45.6 ± 14.7	45.1 ± 15.5	44.7 ± 15.5	45.3 ± 14.7	44.4 ± 14.7	.64

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Estimated GFR (mL/ minute/1.73 m <sup>2</sup> )	45.6 $\pm$ 14.7	45.1 $\pm$ 15.5	44.7 $\pm$ 15.5	45.3 $\pm$ 14.7	44.4 $\pm$ 14.7	.64

# Plant Protein Intake is Associated With Fibroblast Growth Factor 23 and Serum Bicarbonate Levels in Patients With Chronic Kidney Disease: The Chronic Renal Insufficiency Cohort Study

Julia J. Scialla, MD, MHS

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## ▷ Results:

### ▷ Higher percent plant protein was associated with:

- Lower FGF-23
- Higher serum bicarbonate

### ▷ Higher percent plant protein was *not* associated with:

- Higher serum potassium
- Lower serum albumin
- Lower PTH
- Lower hemoglobin

FGF-23 is a hormone that maintains phosphate homeostasis as eGFR decreases.

FGF-23 levels rise earlier in CKD than phosphate.

Is thought to be a more sensitive biomarker for abnormal phosphate metabolism





# Our last patient for the day...

- ▷ 68yo Caucasian man with newly diagnosed Stage 3a CKD. He has many questions about changing his lifestyle.
- ▷ He is wondering if adopting a healthier lifestyle will slow progression of his CKD.
- ▷ What do you tell him?



# Our last patient for the day...

- a) Ideally, he should take up vigorous exercise (~75 mins/week) to protect his renal health.
- b) If he's never smoked, don't start. Never smoking is associated with slower CKD progression.
- c) He should begin a weight loss regimen with the goal of achieving a BMI at the lower limit of normal, i.e., ~ 20.



# Our last patient for the day...

- a) Ideally, he should take up vigorous exercise (~75 mins/week) to protect his renal health.
- b) **If he's never smoked, don't start. Never smoking is associated with slower CKD progression.**
- c) He should begin a weight loss regimen with the goal of achieving a BMI at the lower limit of normal, i.e., ~ 20.



### **Healthy Lifestyle and Risk of Kidney Disease Progression, Atherosclerotic Events, and Death in CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study**

*Ana C. Ricardo, MD,<sup>1</sup> Cheryl A. Anderson, PhD,<sup>2</sup> Wei Yang, PhD,<sup>3</sup> Xiaoming Zhang, MS,<sup>3</sup> Michael J. Fischer, MD,<sup>1,4</sup> Laura M. Dember, MD,<sup>5</sup> Jeffrey C. Fink, MD,<sup>6</sup> Anne Frydrych, RD,<sup>1</sup> Nancy G. Jensvold, MPH,<sup>7</sup> Eva Lustigova, MPH,<sup>8</sup> Lisa C. Nessel, MSS,<sup>3</sup> Anna C. Porter, MD,<sup>1</sup> Mahboob Rahman, MD,<sup>9</sup> Julie A. Wright Nunes, MD,<sup>10</sup> Martha L. Daviglius, MD,<sup>1</sup> and James P. Lash, MD,<sup>1</sup> on behalf of the CRIC Study Investigators\**

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Am J Kidney Dis. 2015;65(3):412-424



## Healthy Lifestyle and Risk of Kidney Disease Progression, Atherosclerotic Events, and Death in CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

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Am J Kidney Dis. 2015;65(3):412-424

- ▷ Study sample: 3,006 participants in CRIC Study
- ▷ Predictors: 4 “Lifestyle Factors”
  - Consuming a “healthy diet”
  - Regular physical activity
  - BMI of 20 to <25
  - Nonsmoking status
- ▷ Outcomes:
  - CKD Progression
  - Atherosclerotic events (MI, stroke, PAD)
  - All-cause mortality



## Healthy Lifestyle and Risk of Kidney Disease Progression, Atherosclerotic Events, and Death in CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

Am J Kidney Dis. 2015;65(3):412-424

### ▷ Consuming a “Healthy Diet”

- Assessed using the Diet History Questionnaire
- 1 point for each of 5 dietary factors adapted from the American Heart Association’s recommendations for cardiovascular health promotion
- Above the median consumption of:
  - Fruits/vegetables (2.8 cups/d)
  - Fish (1.3oz or 37 g/wk)
  - Whole grains (0.88oz or 25 g/d)
- Below the median consumption of:
  - 24-h urine sodium excretion (152mEq/d)
  - Sweets/sugar-sweetened beverages (19.3oz or 571 mL/wk)

Score range 0-5

## Healthy Lifestyle and Risk of Kidney Disease Progression, Atherosclerotic Events, and Death in CKD: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study

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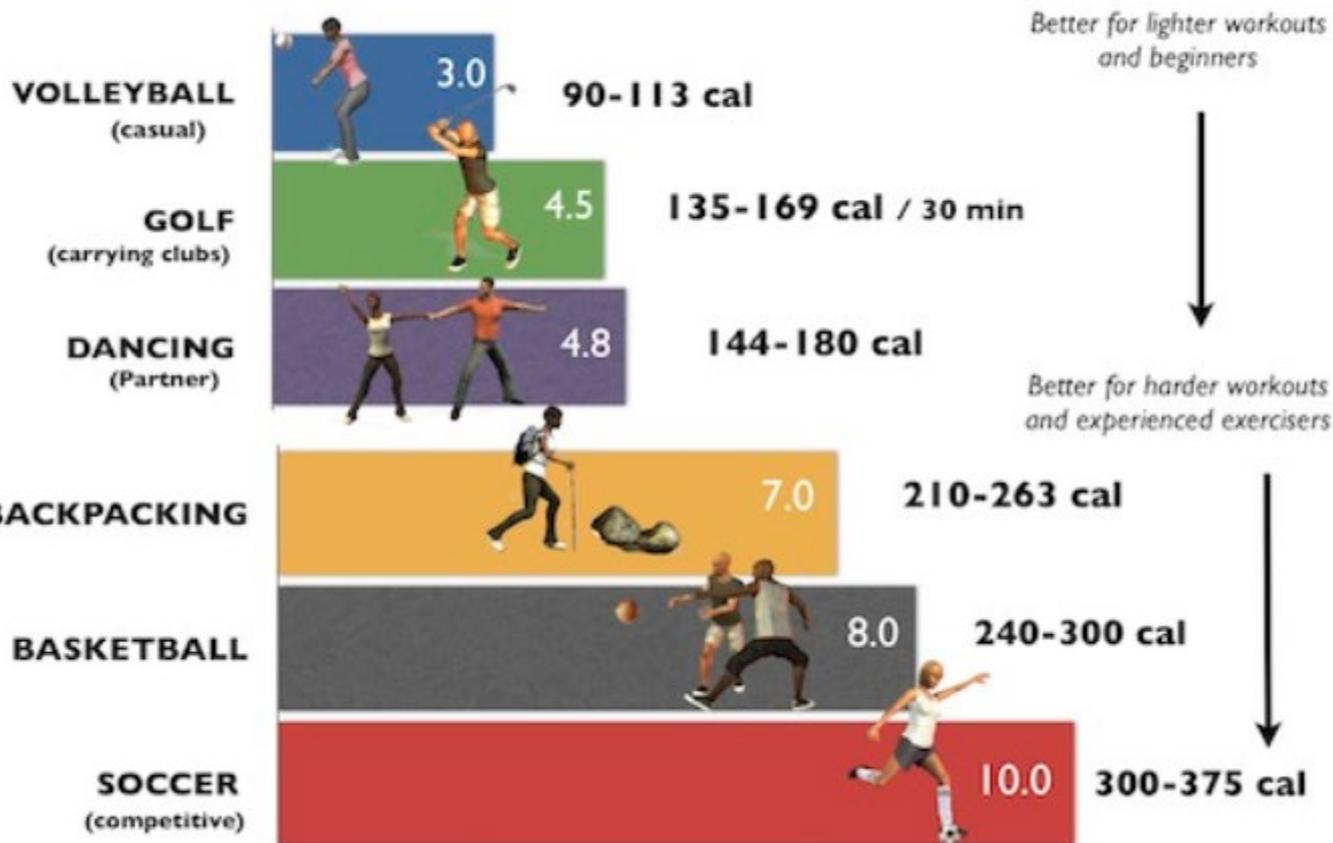
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### ▷ Regular Physical Activity

- Measured using the MESA (Multi-Ethnic Study of Atherosclerosis) Typical Week Physical Activity Survey
- Summarized *intentional* physical activity as a metabolic equivalent task (MET) score (moderate exercise = 3-6 METs, vigorous exercise >6 METs)



# SPORTS and LEISURE



## Ideal:

- Moderate,  $\geq 150$ min/wk
- Vigorous,  $\geq 75$ min/wk
- Moderate + vigorous,  $\geq 150$ min/wk

## < Ideal:

- Not inactive but not meeting criteria for Ideal

## Inactive:

- No reported leisure time physical activity

	BMI					
	<20 kg/m <sup>2</sup> (n = 70)	20-<25 kg/m <sup>2</sup> (n = 430)	25-<30 kg/m <sup>2</sup> (n = 844)	≥30 kg/m <sup>2</sup> (n = 1,662)		
Age (y)	53.75 ± 13.17	55.78 ± 12.77	59.20 ± 10.93	58.53 ± 10.25 <sup>b</sup>		
Female sex	54 (77)	232 (54)	300 (35.5)	848 (51) <sup>b</sup>		
Race/ethnicity						
Non-Hispanic white	35 (50)	238 (55.3)	441 (52.3)	704 (42.4) <sup>b</sup>		
Non-Hispanic black	29 (41)	141 (32.8)	297 (35.2)	854 (51.4)		
Other	6 (9)	51 (11.9)	106 (12.6)	104 (6.3)		
Moderate physical activity (min/wk)	125 [20-360]	180 [15-420]	180 [20-450]	120 [0-360] <sup>b</sup>		
BMI (kg/m <sup>2</sup> )	18.51 ± 1.31	23.01 ± 1.33	27.62 ± 1.42	37.29 ± 6.84 <sup>b</sup>		
Current smoker	24 (34)	86 (20.0)	111 (13.2)	179 (10.8) <sup>b</sup>		
"Healthy diet" score <sup>c</sup>	2.57 ± 1.20	2.60 ± 1.26	2.58 ± 1.17	2.45 ± 1.21 <sup>b</sup>		
	Diet Score					
	0 (n = 129)	1 (n = 501)	2 (n = 873)	3 (n = 848)	4 (n = 524)	5 (n = 131)
Age (y)	54.17 ± 12.24	57.39 ± 11.24	58.14 ± 11.20	58.38 ± 10.85	59.24 ± 10.18	60.45 ± 10.10 <sup>a</sup>
Female sex	50 (38.8)	240 (47.9)	397 (45.5)	420 (49.5)	251 (47.9)	76 (58) <sup>a</sup>
Race/ethnicity						
Non-Hispanic white	56 (43.4)	212 (42.3)	381 (43.6)	435 (51.3)	260 (49.6)	74 (56.5) <sup>a</sup>
Non-Hispanic black	66 (51.2)	252 (50.3)	410 (47)	335 (39.5)	215 (41)	43 (32.8)
Other	7 (5.4)	37 (7.4)	82 (9.4)	78 (9.2)	49 (9.4)	14 (10.7)
Moderate physical activity (min/wk)	140 [0-360]	120 [0-360]	120 [0-360]	140 [0-390]	240 [60-483]	200 [90-420] <sup>a</sup>
BMI (kg/m <sup>2</sup> )	33.45 ± 8.43	32.45 ± 8.18	32.24 ± 8.42	32.38 ± 7.58	31.06 ± 7.53	30.73 ± 7.23 <sup>a</sup>
Current smoker	21 (16.3)	78 (15.6)	135 (15.5)	99 (11.7)	59 (11.3)	8 (6.1) <sup>a</sup>
"Healthy diet" score <sup>b</sup>	0	1.00 ± 0.00	2.00 ± 0	3.00 ± 0	4.00 ± 0	5.00 ± 0 <sup>a</sup>

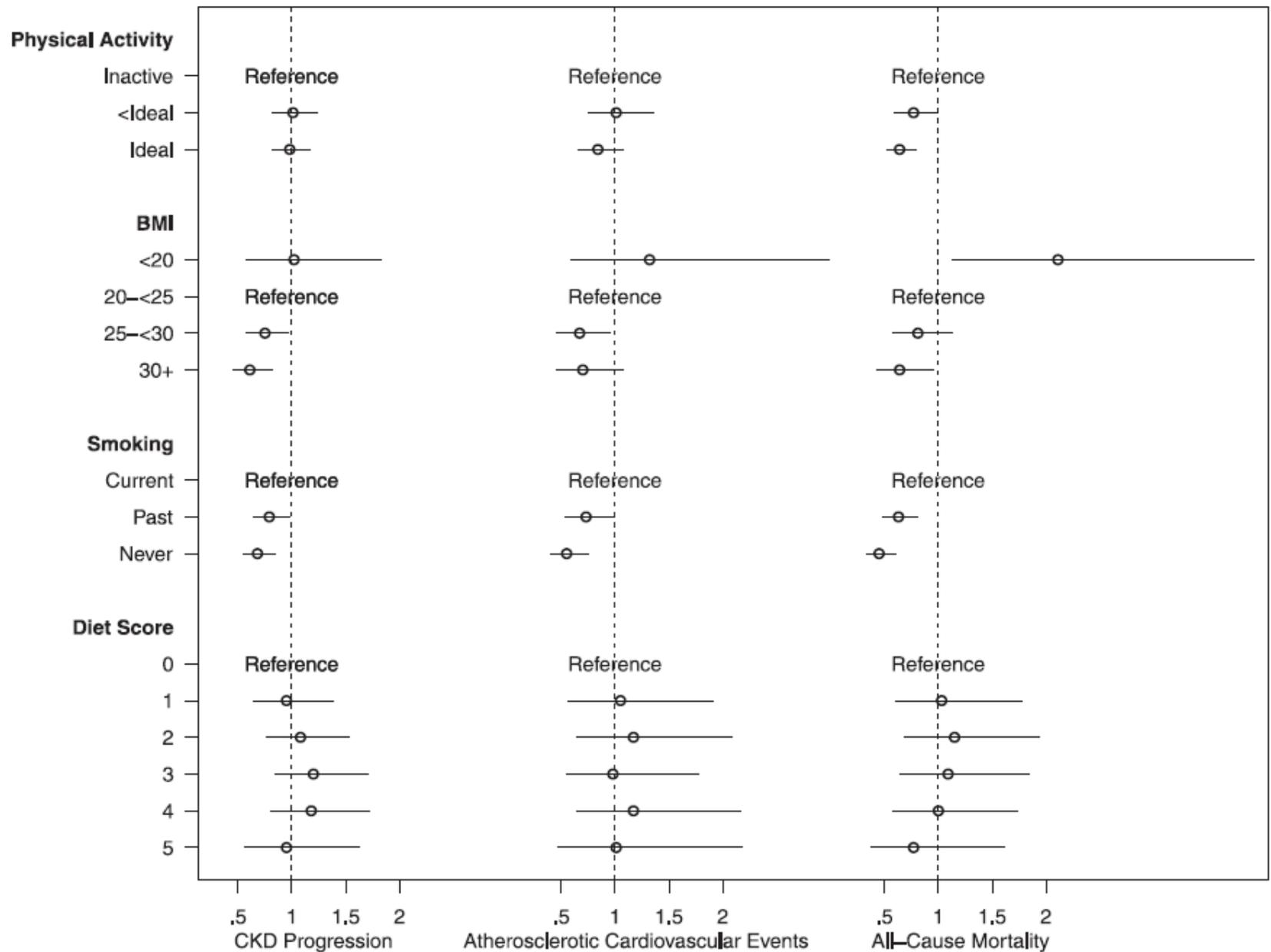
Diet abundant in fruits, vegetables, whole grains, and fish and low in sodium and sweets.



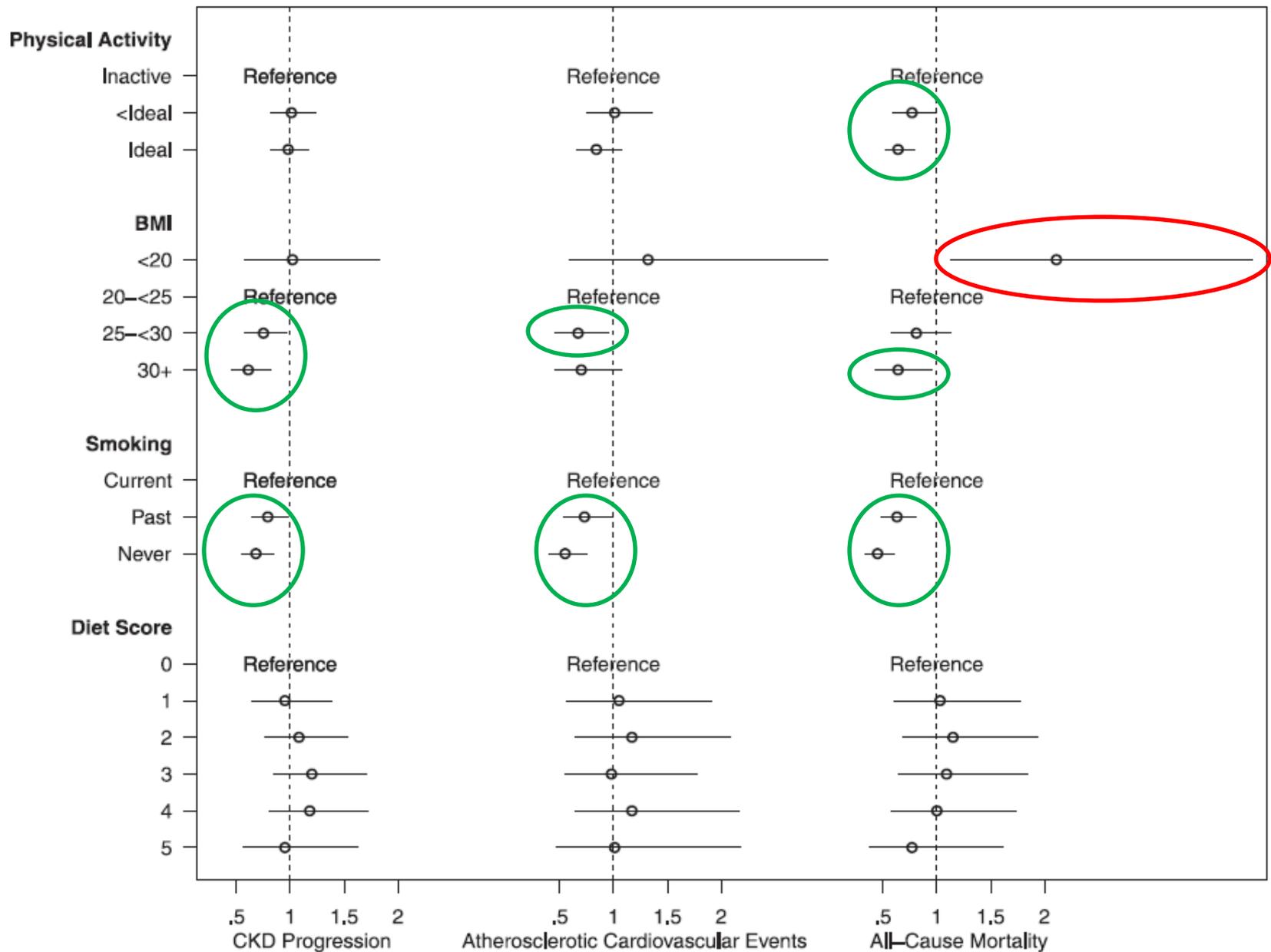
	Physical Activity <sup>a</sup>		
	Inactive (n = 849)	<Ideal (n = 565)	Ideal (n = 1,592)
Age (y)	60.06 ± 10.11	58.34 ± 10.92	57.16 ± 11.33 <sup>b</sup>
Female sex	443 (52.2)	296 (52.4)	695 (43.7) <sup>b</sup>
Race/ethnicity			
Non-Hispanic white	368 (43.3)	262 (46.4)	788 (49.5) <sup>b</sup>
Non-Hispanic black	426 (50.2)	237 (41.9)	658 (41.3)
Other	55 (6.5)	66 (11.7)	146 (9.2)
Moderate physical activity (min/wk)	0	80 [55-120]	375 [233-640] <sup>b</sup>
BMI (kg/m <sup>2</sup> )	34.10 ± 9.21	31.98 ± 7.63	31.06 ± 7.13 <sup>b</sup>
Current smoker	148 (17.4)	87 (15.4)	165 (10.4) <sup>b</sup>
"Healthy diet" score <sup>c</sup>	2.28 ± 1.14	2.55 ± 1.17	2.61 ± 1.23 <sup>b</sup>
	Smoking Status		
	Current (n = 400)	Past (n = 1,259)	Never (n = 1,347)
Age (y)	55.94 ± 10.12	61.04 ± 9.38	56.23 ± 12.00 <sup>a</sup>
Female sex	194 (48.5)	515 (40.9)	725 (53.8) <sup>a</sup>
Race/ethnicity			
Non-Hispanic white	128 (32)	648 (51.5)	642 (47.7) <sup>a</sup>
Non-Hispanic black	257 (64.3)	506 (40.2)	558 (41.4)
Other	15 (3.8)	105 (8.3)	147 (10.9)
Moderate physical activity (min/wk)	60 [0-315]	140 [0-375]	180 [10-420] <sup>a</sup>
BMI (kg/m <sup>2</sup> )	29.96 ± 7.56	32.25 ± 7.51	32.58 ± 8.39 <sup>a</sup>
Current smoker	400 (100)	0 (0)	0 (0) <sup>a</sup>
"Healthy diet" score <sup>b</sup>	2.30 ± 1.16	2.53 ± 1.17	2.55 ± 1.24 <sup>a</sup>



**Figure 1.** Multivariable-adjusted hazard ratios and 95% confidence intervals of outcomes.



**Figure 1.** Multivariable-adjusted hazard ratios and 95% confidence intervals of outcomes.



# Our last patient for the day...

- a) Ideally, he should take up vigorous exercise (~75 mins/week) to protect his renal health.
- b) **If he's never smoked, don't start. Never smoking is associated with slower CKD progression.**
- c) He should begin a weight loss regimen with the goal of achieving a BMI at the lower limit of normal, i.e., ~ 20.



# Objectives

1. Review the CRIC Study and its purpose
2. Understand the type of information that is collected from participants during their visits.
3. Review recent CRIC Study Publications in a case-based format



# Acknowledgements

- ▷ Illinois Council on Renal Nutrition
- ▷ Sincere *thank you* to all the CRIC Study participants and the CRIC Study staff at UIC



# Thank you!

## Any questions?

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