

CKD Epidemiology

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**CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE**



**HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL**

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University College Cork
Residency @ Beaumont Hospital, Dublin
Renal Fellowship @ BWH
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Clinical Focus

- Lupus Nephritis
- ICU Nephrology

Disclosure

- Consultant for Apellis Pharma, Fresenius Healthcare
- Research Support from Alexion Pharmaceuticals.

Objective

- Discuss the definition, diagnosis and prevalence of CKD
- Convince you that early-stage CKD is important.
- Discuss strategies to reduce progression of CKD

Question

- A 65yo woman with a history of diabetes and hypertension presents for evaluation. Her serum creatinine is 1.0mg/dl and her Cystatin C is 1.2mg/dl. Which of the following GFR estimating equations best predicts her likelihood of cardiovascular mortality based on CKD category?
- A. Cockcroft-Gault
- B. MDRD
- C. CKD-EPI Cystatin-C
- D. CKD-EPI Creatinine
- E. CKD-EPI Creatinine-Cystatin C

Question

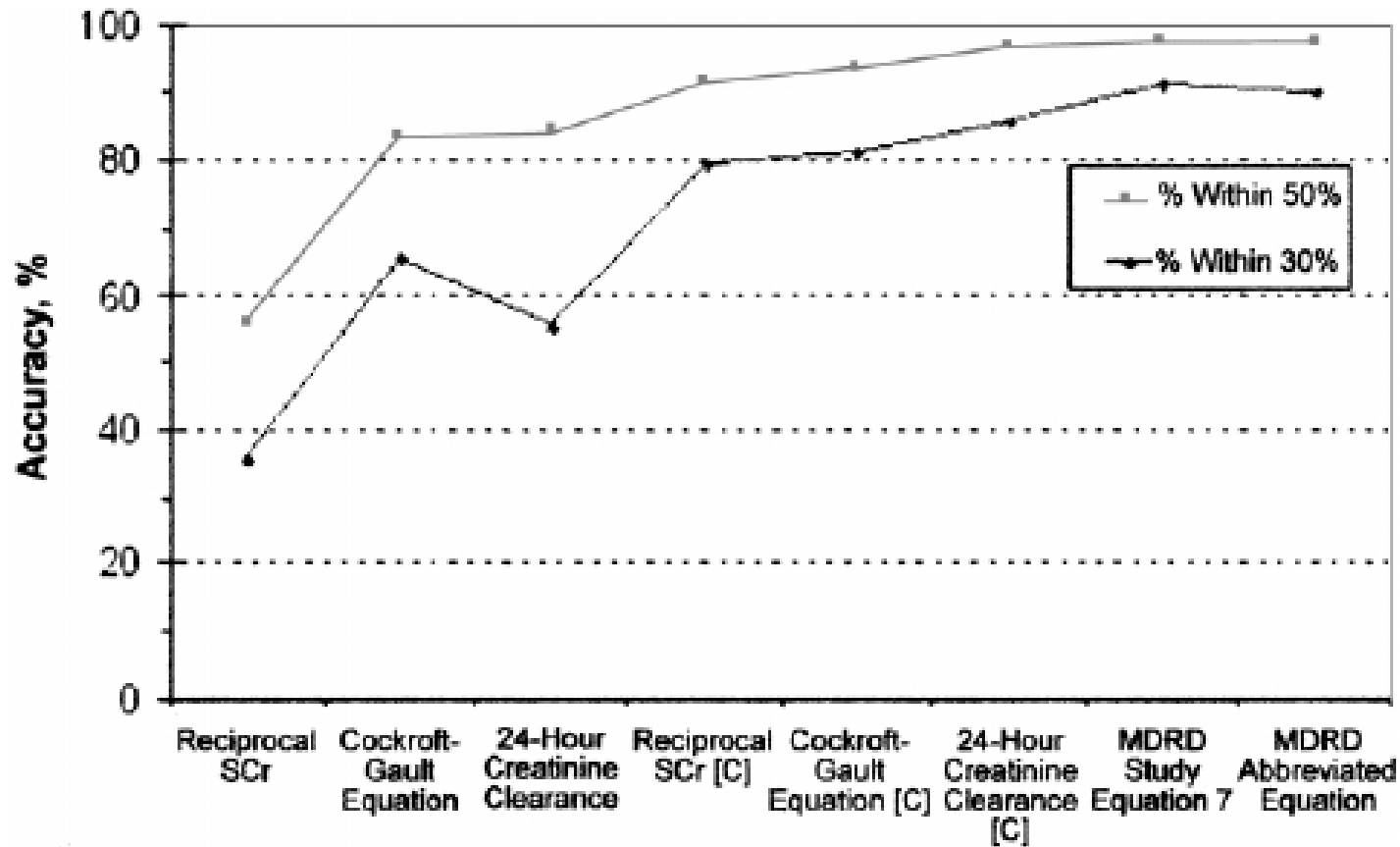
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**How do we measure kidney
function?**

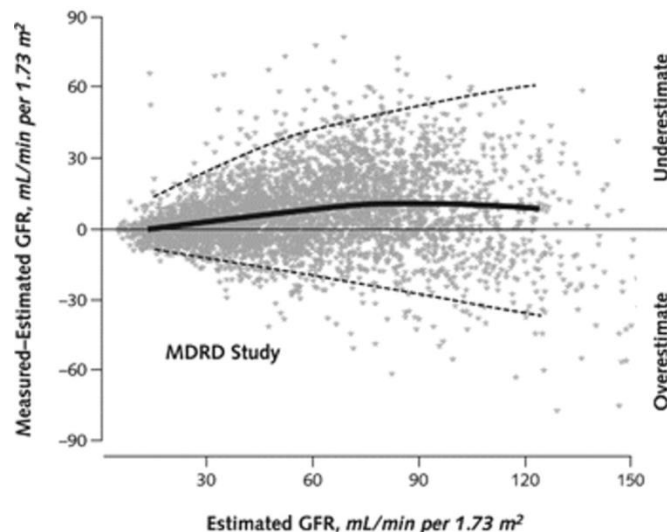
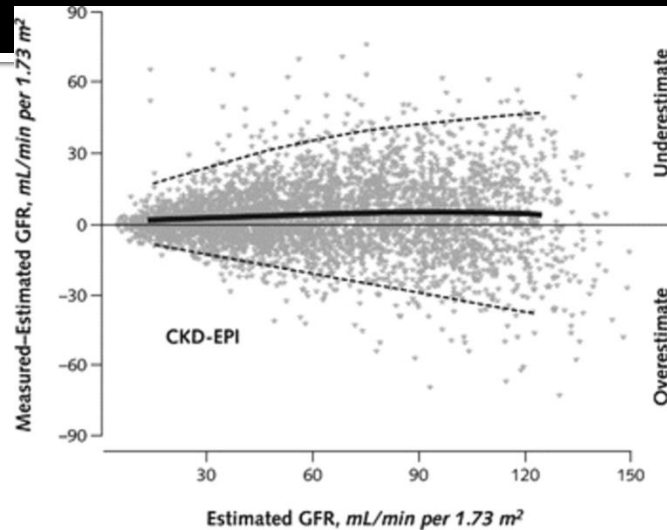
GFR Measurement and Estimation

Method	Description	Advantages	Potential Limitations
Measured GFR	•Urinary clearance of an exogenous or endogenous filtration marker. •Plasma clearance of an exogenous filtration marker.	•Accurate (gold standard methods)	•Inconvenient to patients •Expensive •Not suitable for population-based screening
Estimated GFR	•Equations based on serum levels of filtration markers (creatinine/cystatin C)	•Suitable for population screening •Rapid result (single measurement) •Inexpensive	•Non-GFR determinants of marker concentrations •Assay variation •Inaccurate particularly in non-steady state situations (AKI)

Accuracy of Commonly Used Methods for Estimating GFR



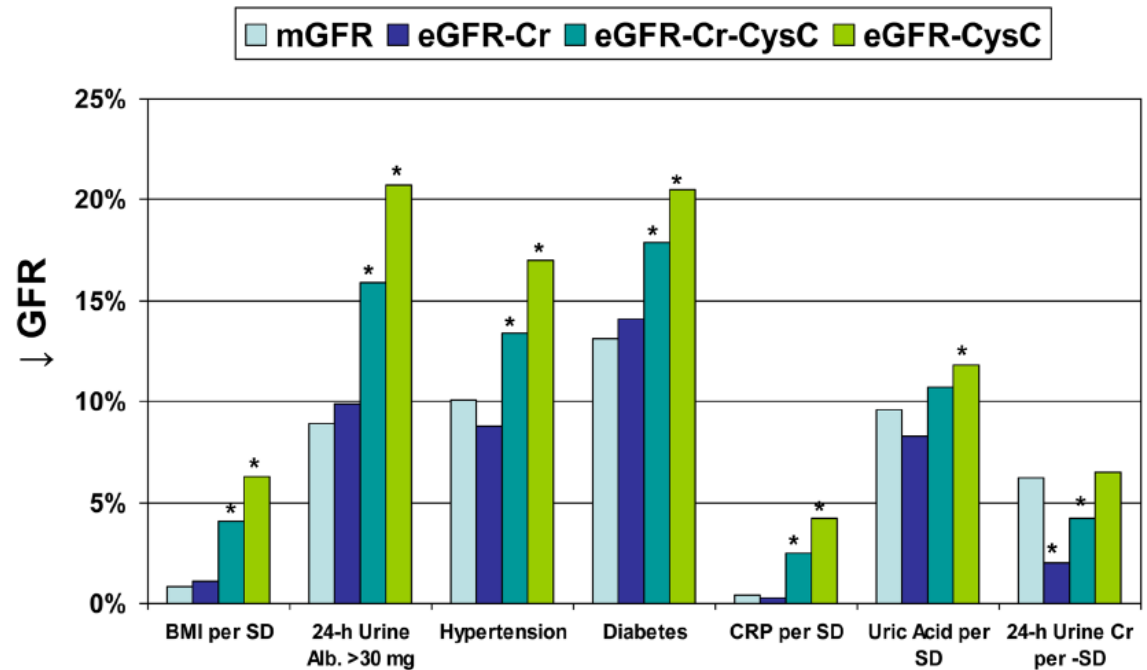
CKD-Epi Equation



- KDIGO recommends using the CKD-Epi equation in clinical practice and for research.
- Compared to MDRD
 - Less Bias
 - More accurate
 - Improved risk reclassification
- Approximately 84% of measurements within 30% of the true (measured GFR)

Cystatin C

- Significant non-GFR determinants of Cystatin C
 - Male Sex
 - Greater height and weight
 - Higher lean body mass
 - Higher fat mass
 - Diabetes
 - Higher inflammatory markers
 - Inflammation in general
 - Hypothyroidism
 - Steroid use



Rule et al, *Kid Int* 2013

Accuracy of eGFR in Individuals

- eGFR was never designed for individual-level decision-making.
- Mean difference between mGFR and eGFR_{cr} was 0.6ml/min
- Wide range of values for individuals at a given eGFR
- No improvement with eGFR_{cys}
- Likely should be reported as a range rather than a single number

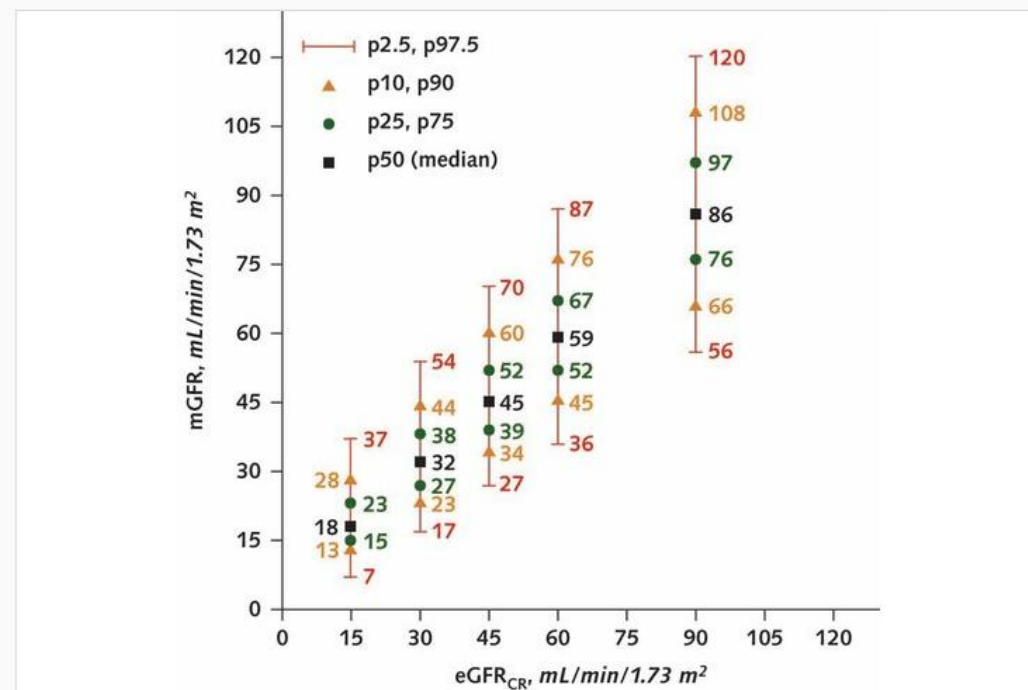


Figure 1. Distribution of mGFR at selected eGFR_{CR} thresholds in 3223 participants of 4 cohort studies.

Should we adjust for race when calculating eGFR?

VIEWPOINT

Reconsidering the Consequences of Using Race to Estimate Kidney Function

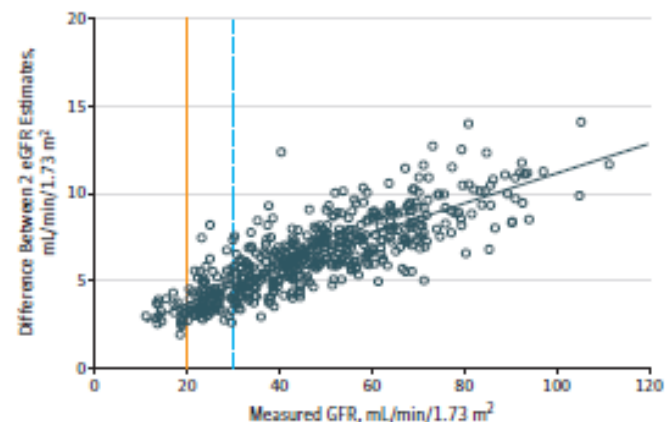
Nwamaka Denise
Eneanya, MD, MPH

Clinicians estimate kidney function to guide important medical decisions across a wide range of settings,

mutations like sickle cell trait or cystic fibrosis. However, eGFR equations are distinct because they instead

- Minor improvement in estimation on a population basis
- Unclear how much more accurate on individual basis
- Forces doctors to make value judgements about race based on appearance
- Likely that other factors are responsible for the difference

Figure. Relationship Between Racial Categories and Estimation of Kidney Function Across the Spectrum of Chronic Kidney Disease



Should we adjust for race when calculating eGFR?

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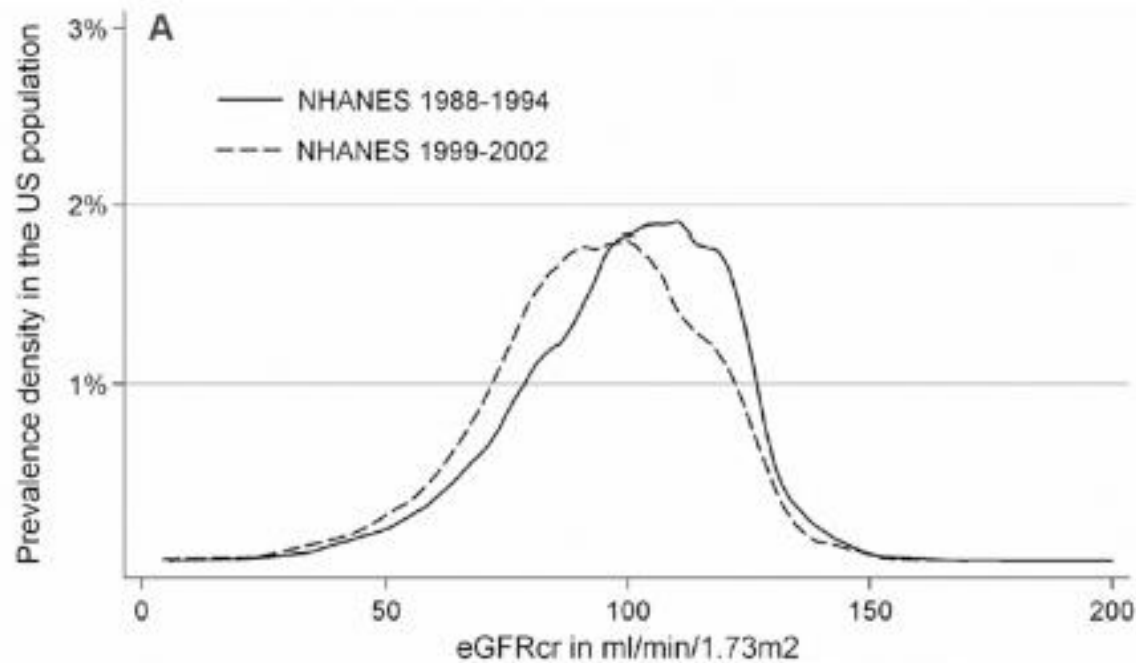
VOL. 385 NO. 19

New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

L.A. Inker, N.D. Eneanya, J. Coresh, H. Tighiouart, D. Wang, Y. Sang, D.C. Crews, A. Doria, M.M. Estrella, M. Froissart, M.E. Grams, T. Greene, A. Grubb, V. Gudnason, O.M. Gutiérrez, R. Kalil, A.B. Karger, M. Mauer, G. Navis, R.G. Nelson, E.D. Poggio, R. Rodby, P. Rossing, A.D. Rule, E. Selvin, J.C. Seegmiller, M.G. Shlipak, V.E. Torres, W. Yang, S.H. Ballew, S.J. Couture, N.R. Powe, and A.S. Levey, for the Chronic Kidney Disease Epidemiology Collaboration*

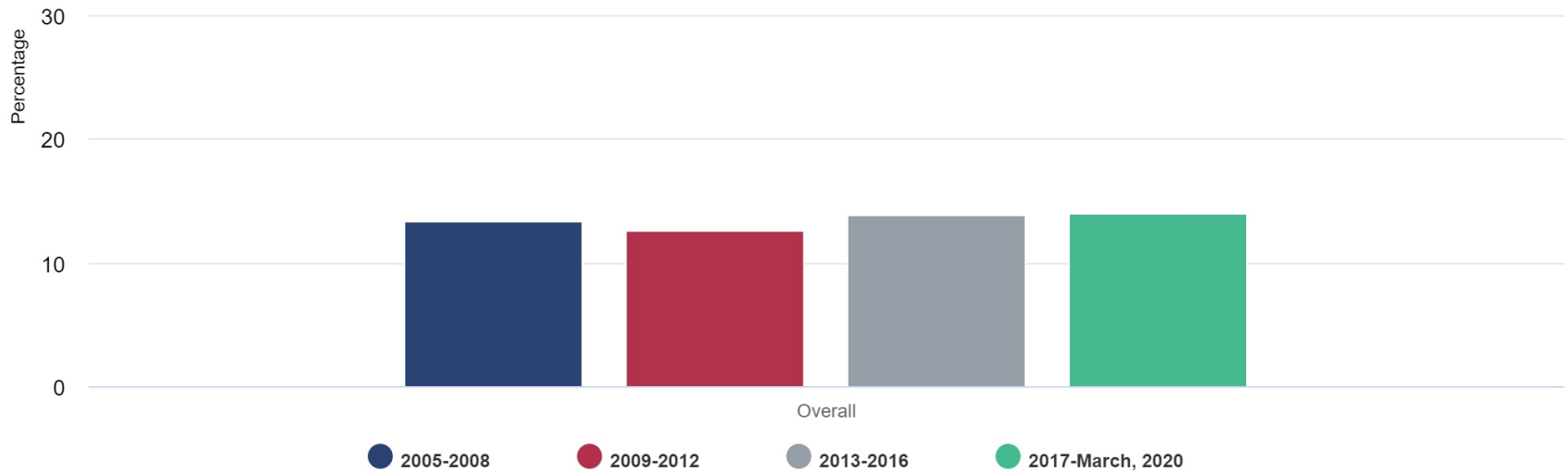
How common is CKD?

Prevalence of CKD



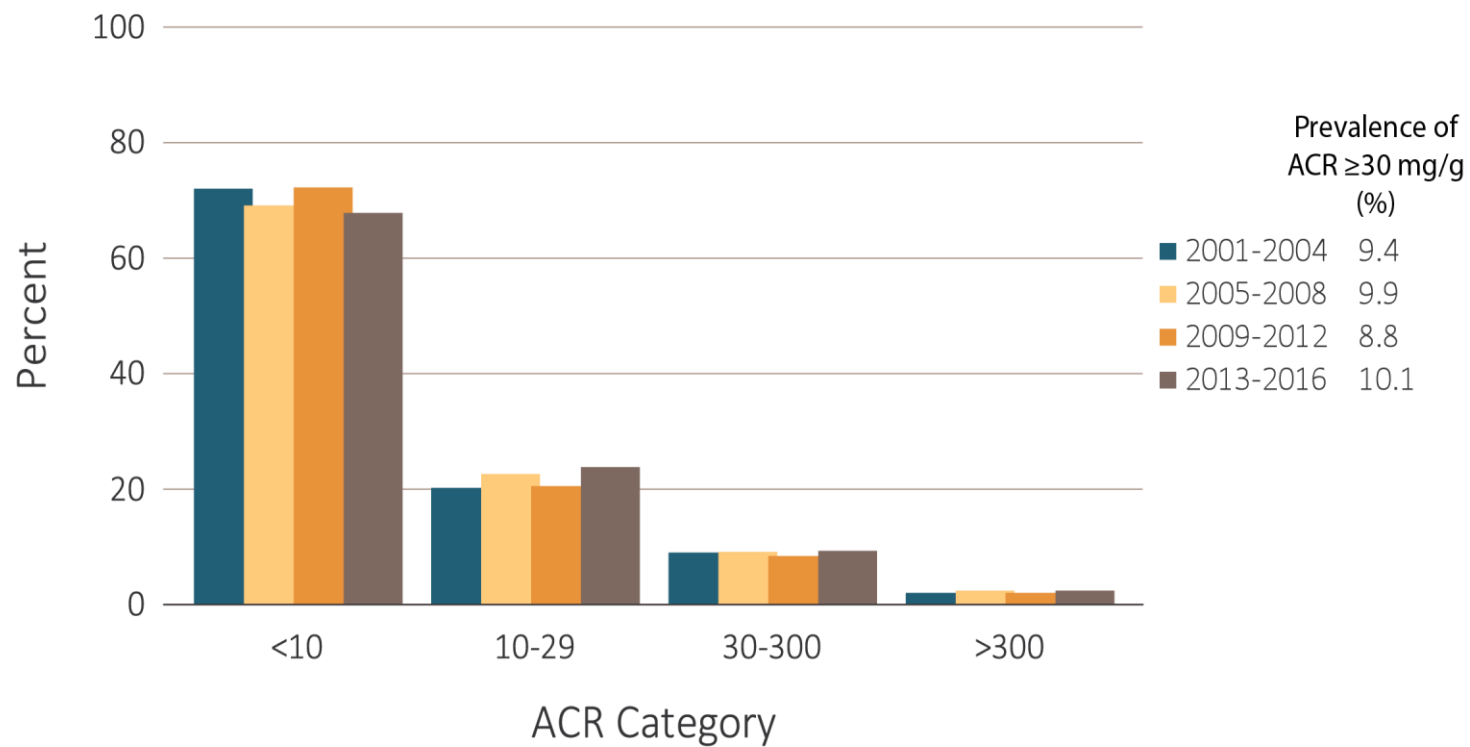
NHANES	Prevalence (%)
1988-1994	4.7
1999-2002	6.5
2001-2002	8.1
2009-2010	7.8

Prevalence of CKD in US Adults

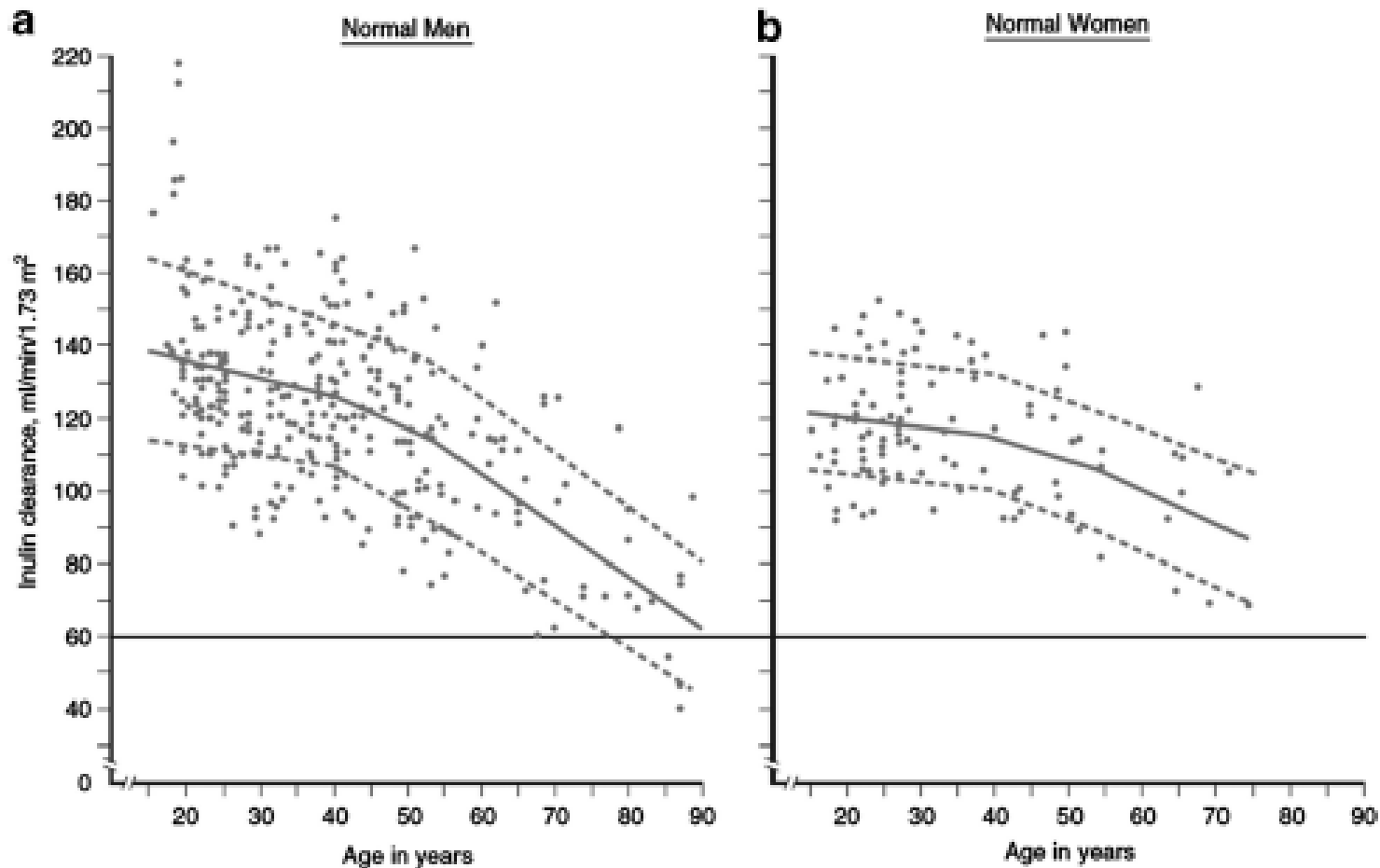


14% prevalence of CKD in adults in most recent NHANES survey

Prevalence of albuminuria

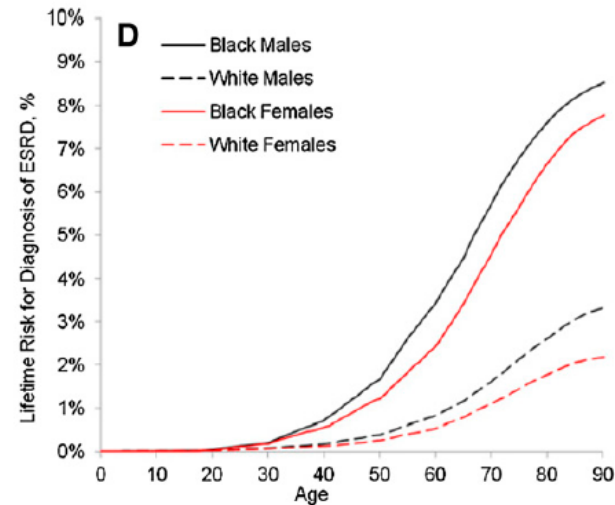
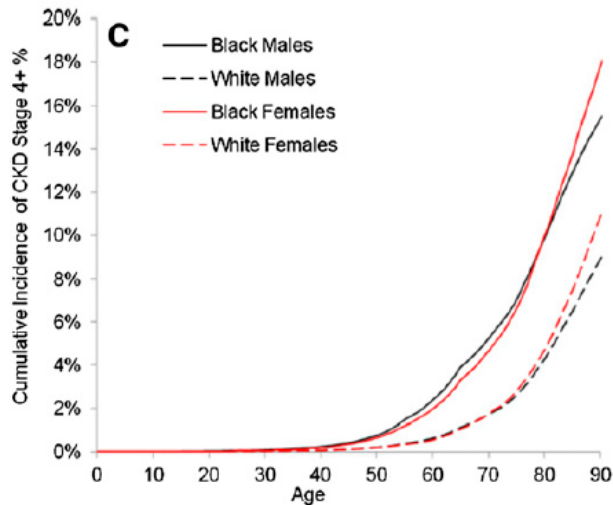
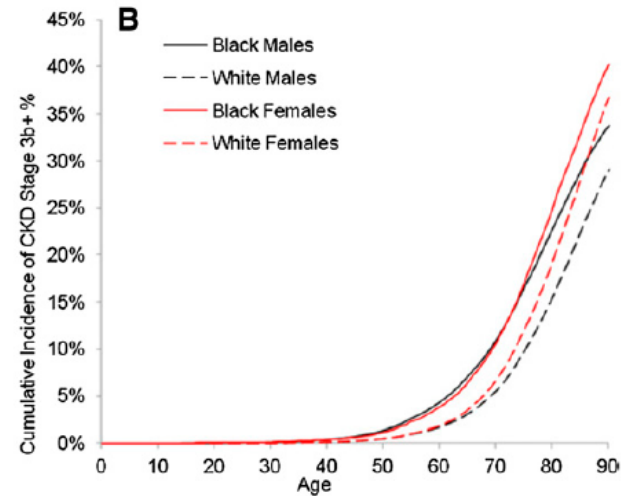
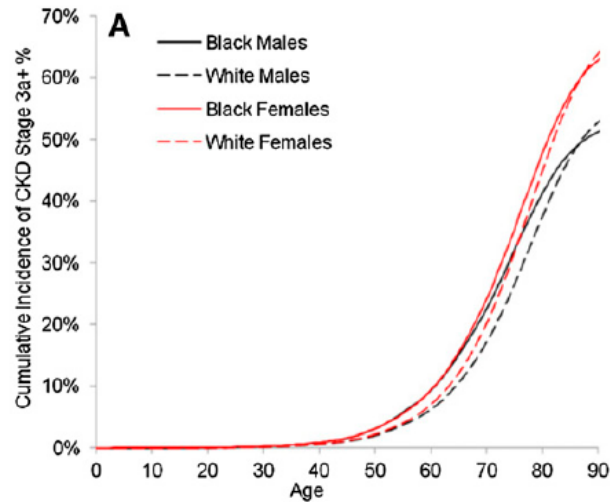


Increasing Prevalence of CKD with Age

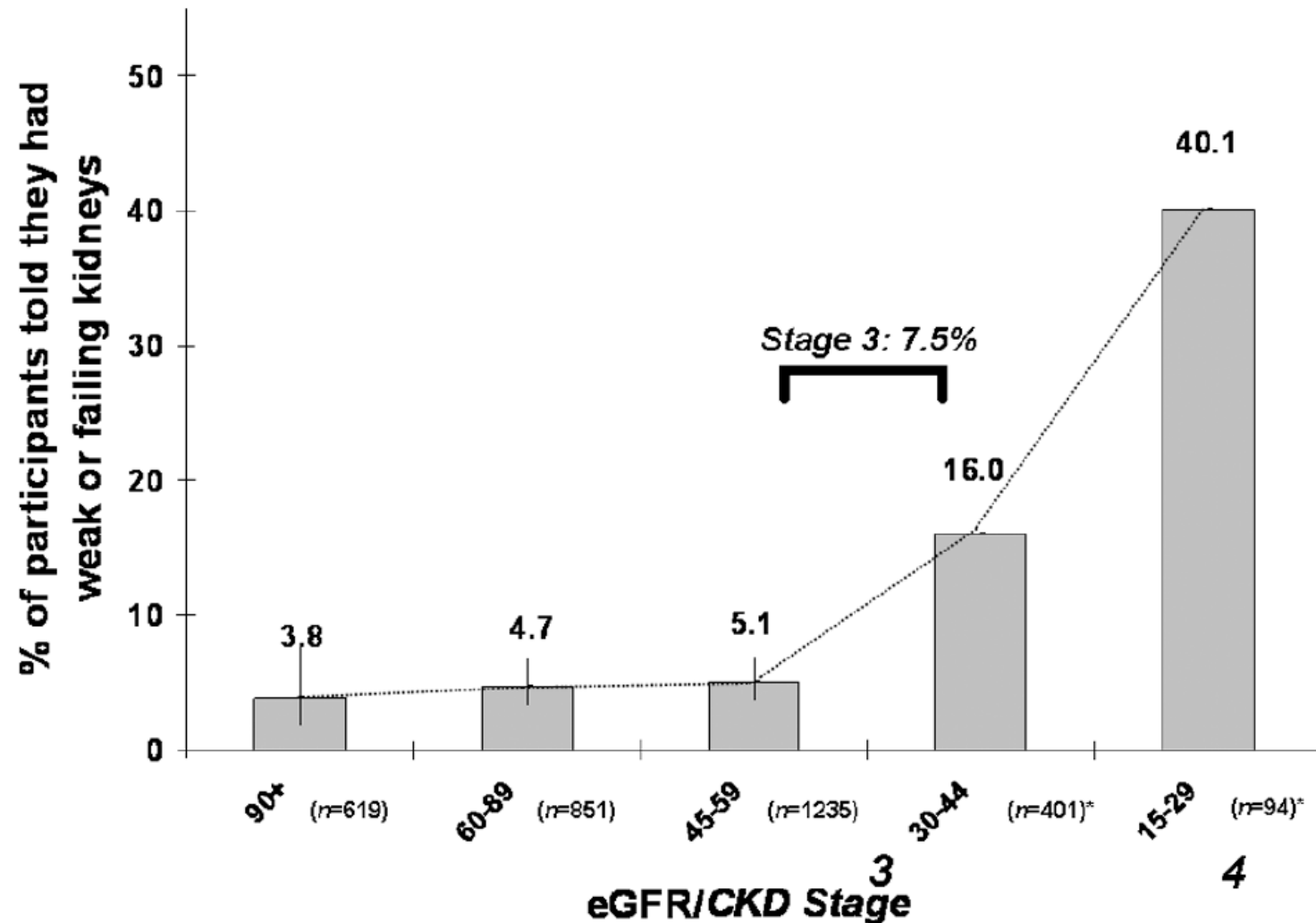


Wesson et al, *Physiology of the Human Kidney* 1969

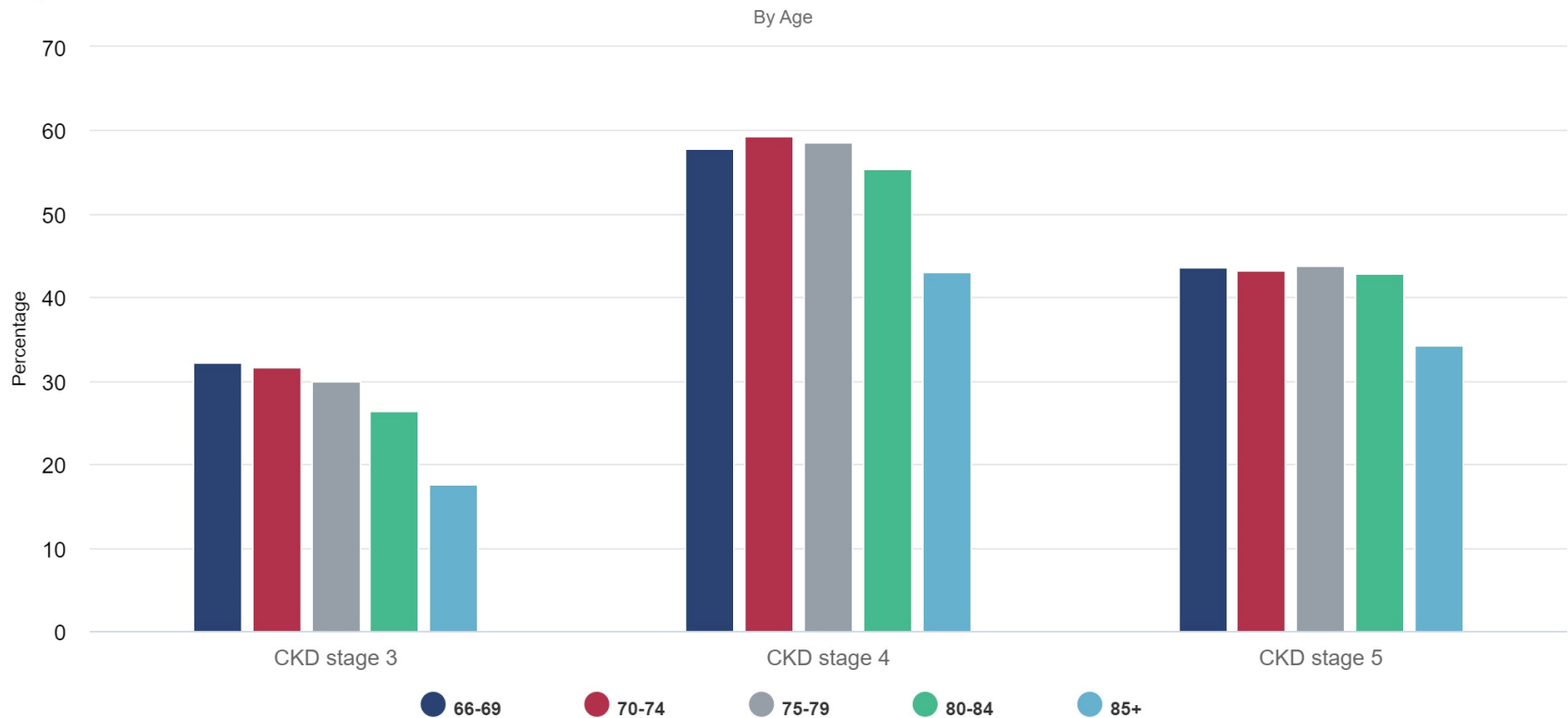
Lifetime Risk of CKD



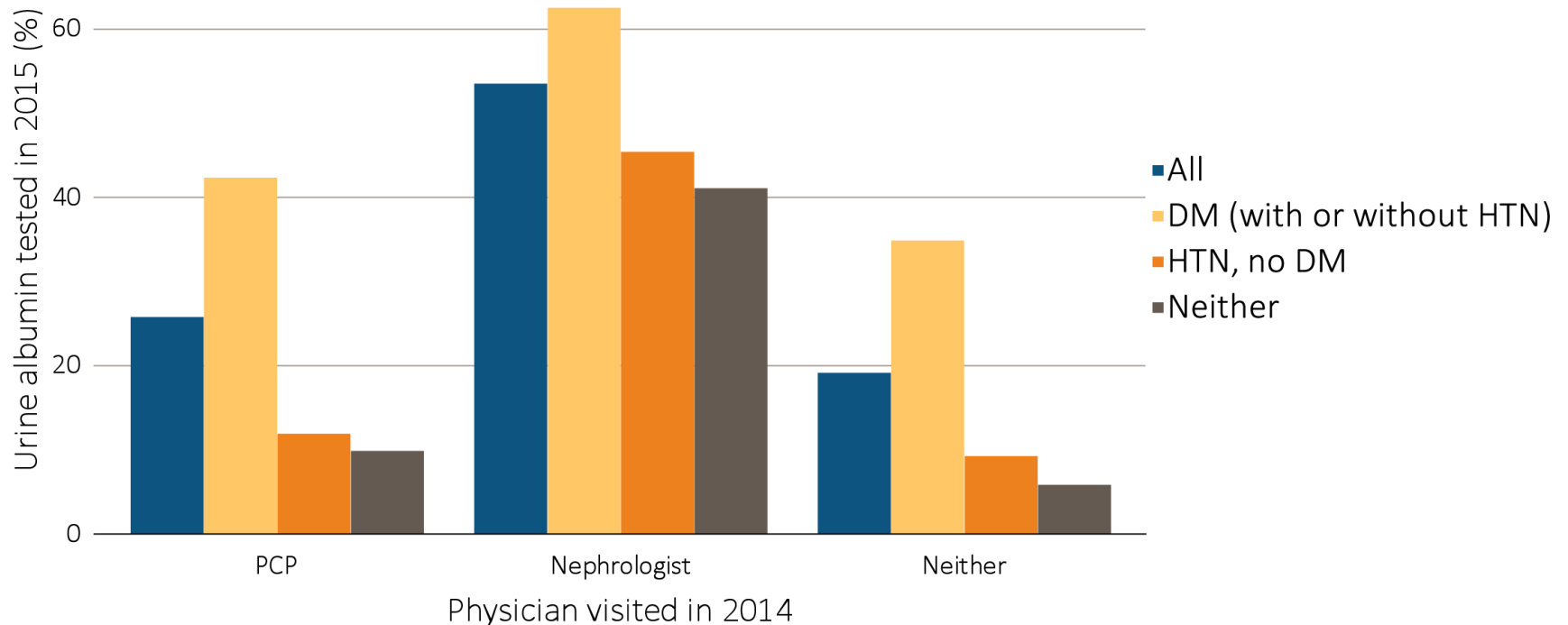
Poor awareness of CKD



Low referral rates to nephrology particularly in the elderly



Poor awareness of CKD among physicians



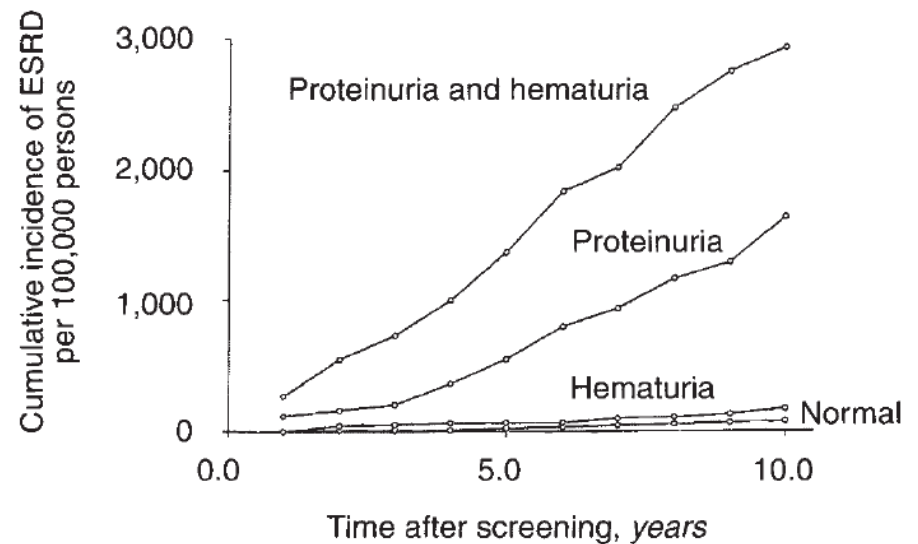
Is early CKD important?

Asymptomatic Hematuria and the Risk of ESRD

- 1.2 million Israeli army candidates (60% male), aged 16-25
- Dipstick hematuria, confirmed by microscopy
- Normal GFR, no proteinuria, normal u/s.
- Asymptomatic microscopic hematuria as judged by nephrologist present in 0.3% of candidates
- Increased ESRD rates on 20 year follow up:
 - 34.0 vs. 2.05 per 100,000 person years
 - HR 18.5 (12.4-27.6)
- ESRD due to primary glomerular disease: HR 32.4 (18.9-55.7)

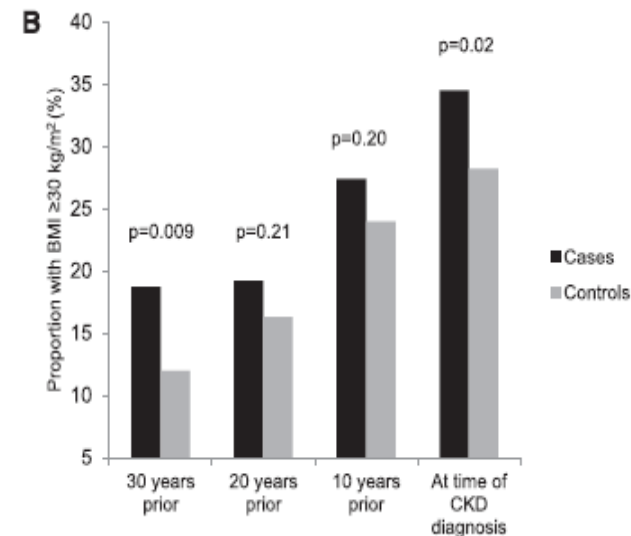
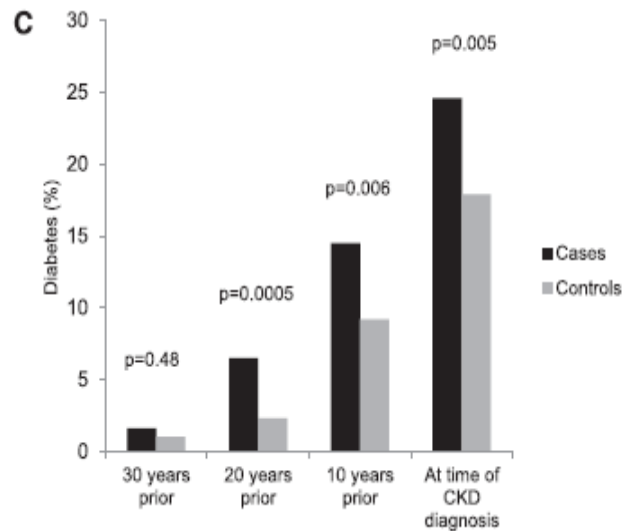
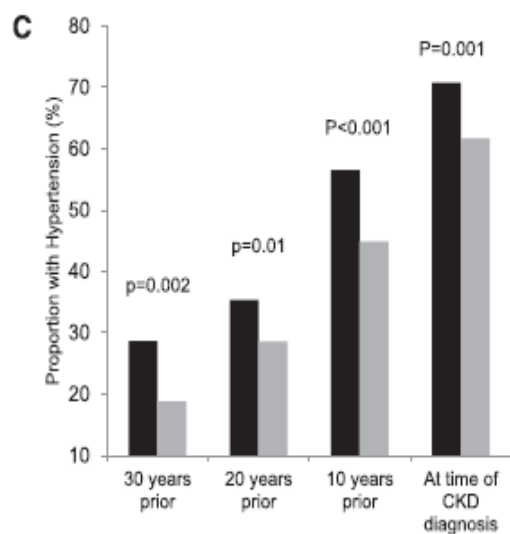
Risk of developing ESKD in a screening cohort

- >107,000 subjects, single dipstick UA & BP check
- 10 year follow up; 193 ESKD patients identified
- Dipstick proteinuria OR: 14.9 (10.9-20.2)
- Hematuria OR: 2.3 (1.62-3.3)
- Male OR: 1.41 (1.04-1.92)
- DBP OR: 1.39 (1.17-1.64) per 10mmHg

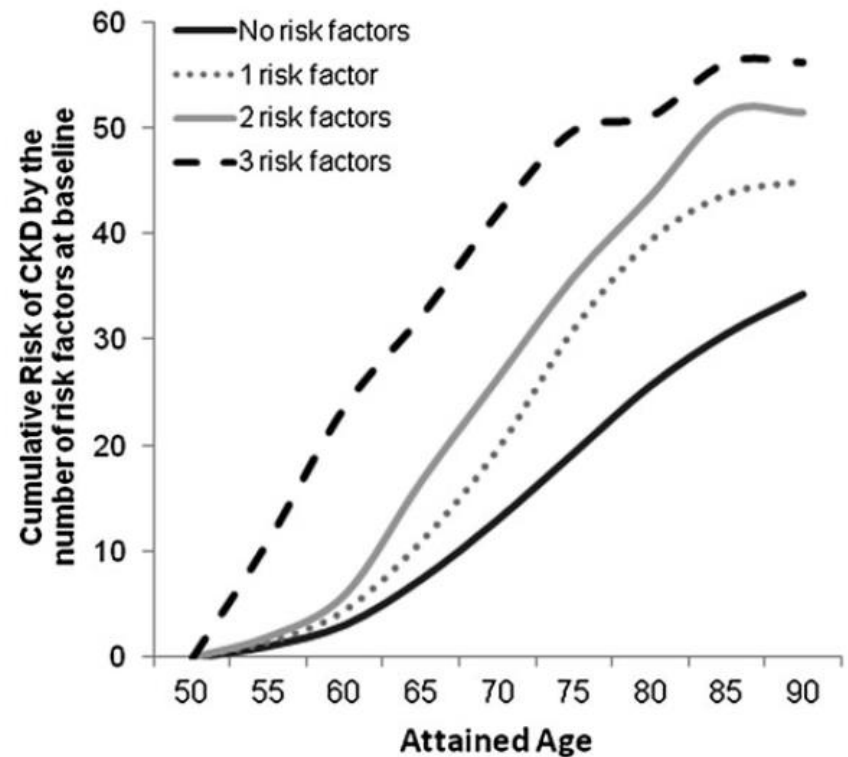
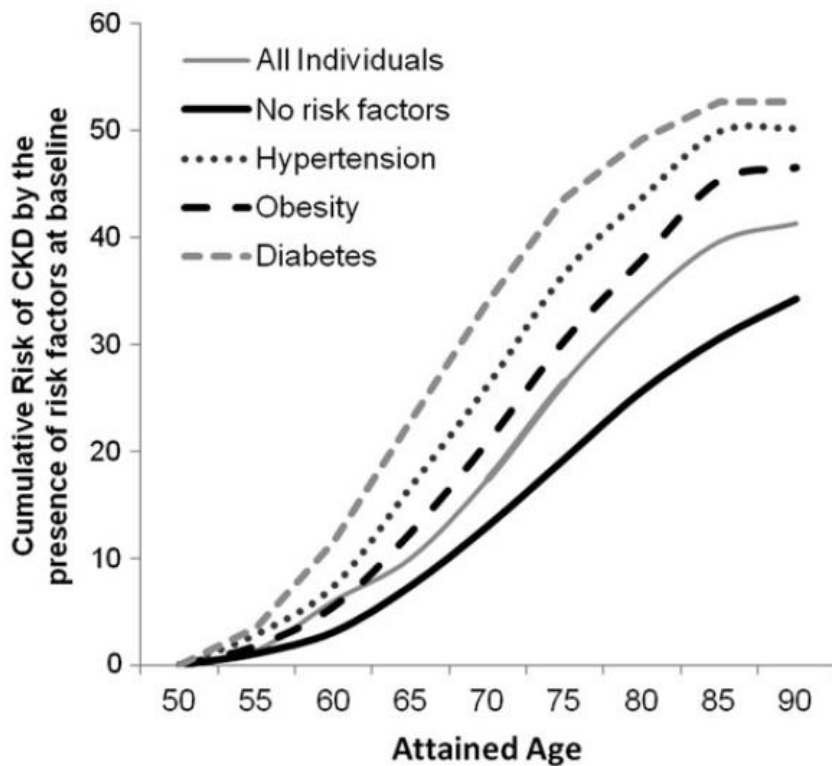


Iseki et al. KI 1996, 49(3): 800

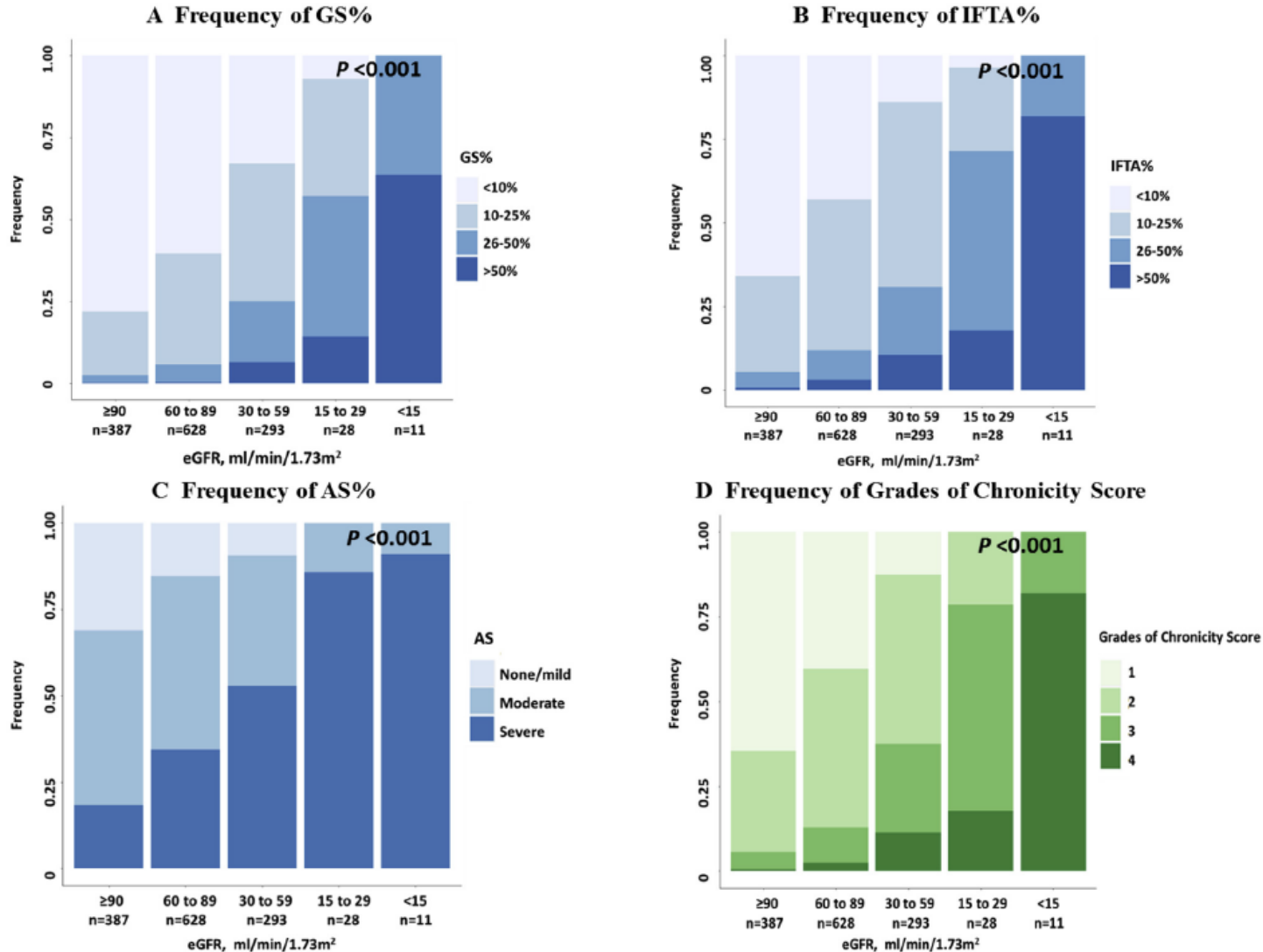
Long-term Risk Factors for CKD



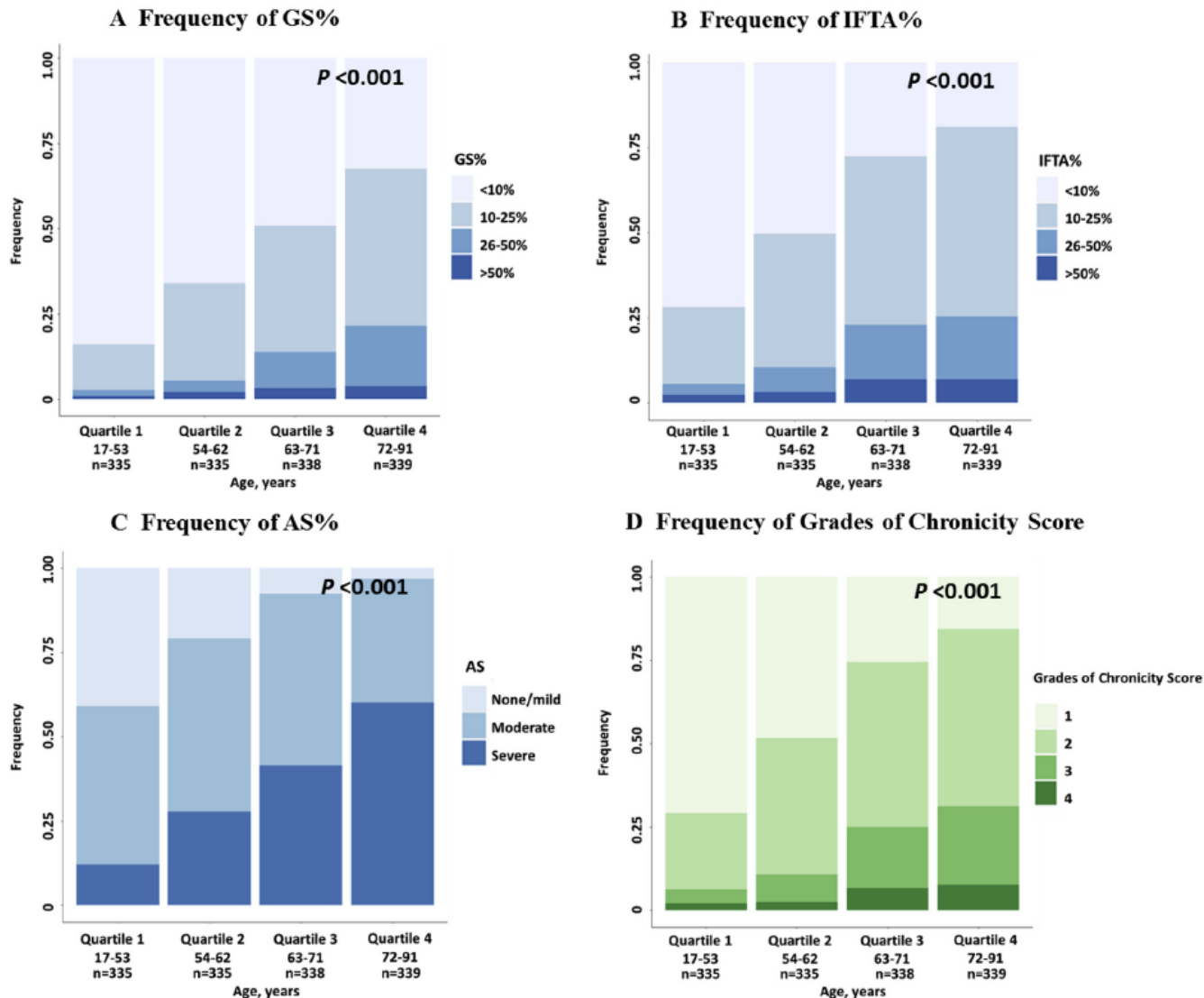
Residual Lifetime Risk of CKD



Distinct pathologic profile in patients with early CKD – GFR categories



Distinct pathologic profile in patients with early CKD – changes with age



Complications develop early in CKD

Table 27 | Prevalence of CKD complications by GFR category* derived from CKD cohorts

Complication	GFR category (ml/min/1.73 m ²)					Reference
	≥ 90	60-89	45-59	30-44	< 30	
Anemia ¹	4.0%	4.7%	12.3%	22.7%	51.5%	366
Hypertension ²	18.3%	41.0%	71.8%	78.3%	82.1%	366
25(OH) Vit D deficiency ³	14.1%	9.1%	10.7%		27.2%	367
Acidosis ⁴	11.2%	8.4%	9.4%	18.1%	31.5%	366
Hyperphosphatemia ⁵	7.2%	7.4%	9.2%	9.3%	23.0%	366
Hypoalbuminemia ⁶	1.0%	1.3%	2.8%	9.0%	7.5%	366
Hyperparathyroidism ⁷	5.5%	9.4%	23.0%	44.0%	72.5%	366

The logo features a stylized globe icon composed of a grid of blue and white lines, representing the Earth. It is positioned to the left of the project name.

KIDNEY PRECISION MEDICINE PROJECT

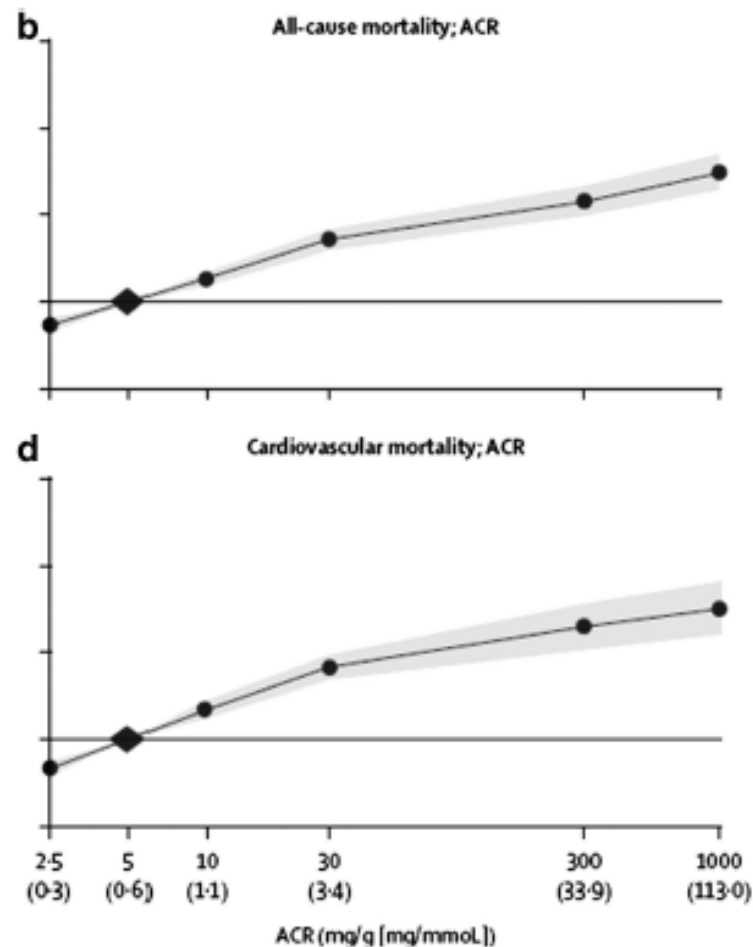
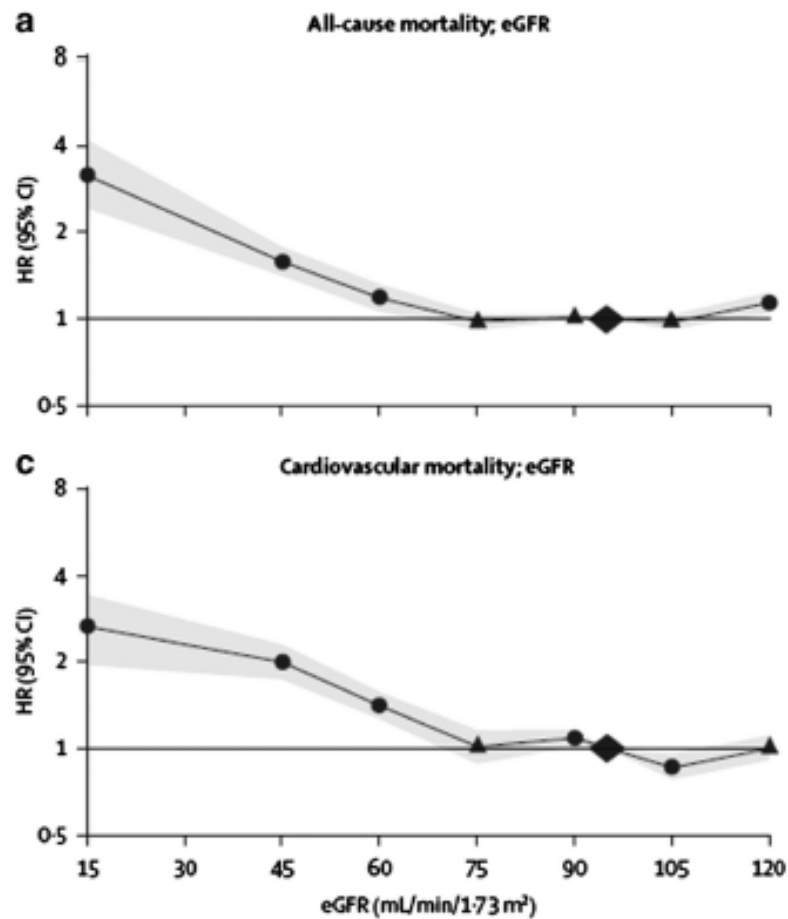
- Multicenter study recruiting patients with AKI and early CKD for research kidney biopsies.
- Establish an atlas of kidney disease
- 15 recruitment sites – AKI, DM1, CKD
- 5 tissue interrogation sites in US and Europe
- Hypertension or diabetes with CKD or albuminuria
- Avoid patients with likely glomerular disease



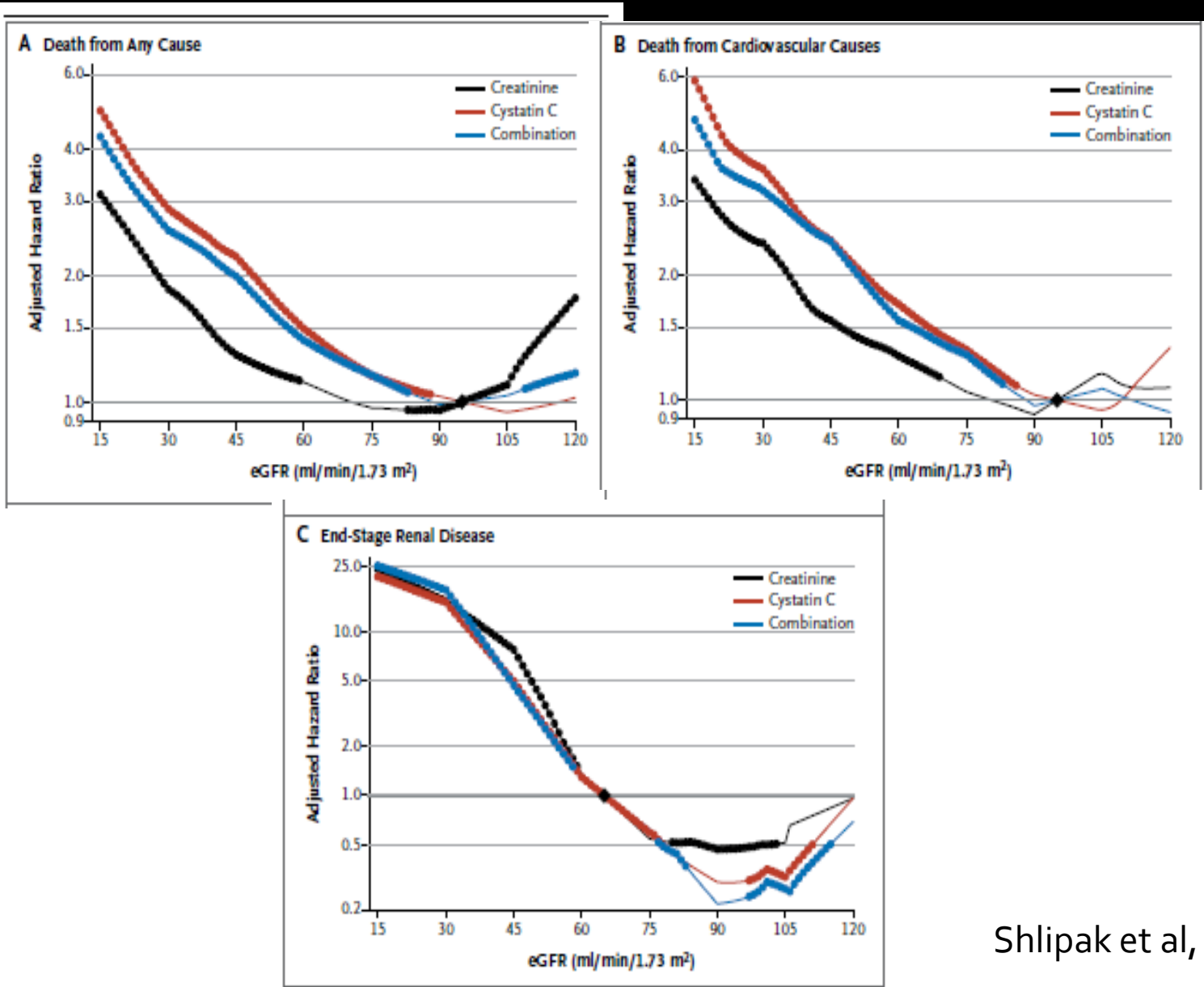
- CKD Adjudication
 - Pathologic language aimed at describing acute glomerular processes primarily
 - Poor at describing tubulointerstitial changes and their significance
 - Significant “acute tubular injury” in CKD patients with no history of AKI
 - Confirmation bias appears to play a major role in describing indeterminate lesions e.g. early diabetic nephropathy.
- Need to develop a new way of thinking about and describing CKD biopsies.
- Increase the frequency of biopsies in this population
- Develop new biomarkers of CKD progression.

**What are the real world
consequences of early CKD?**

CKD and Cardiovascular Disease



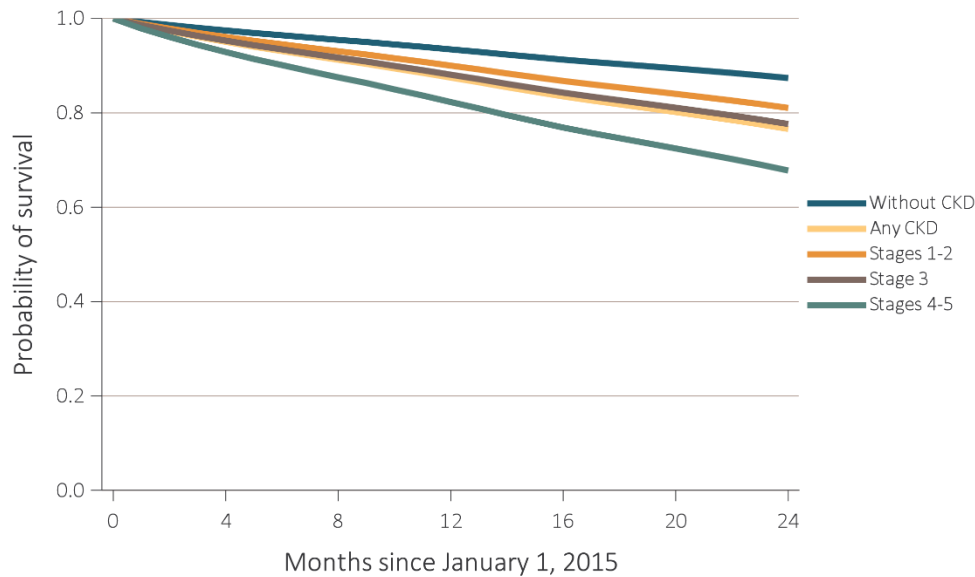
Cystatin C is a better predictor of CVD



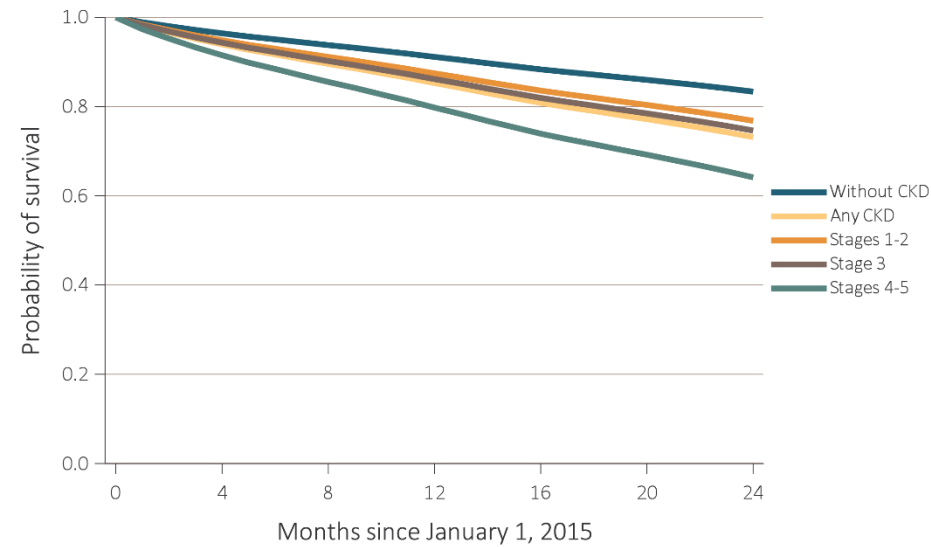
Shlipak et al, *NEJM* 2013

CKD Increases mortality in CVD

Acute MI



CVA/TIA



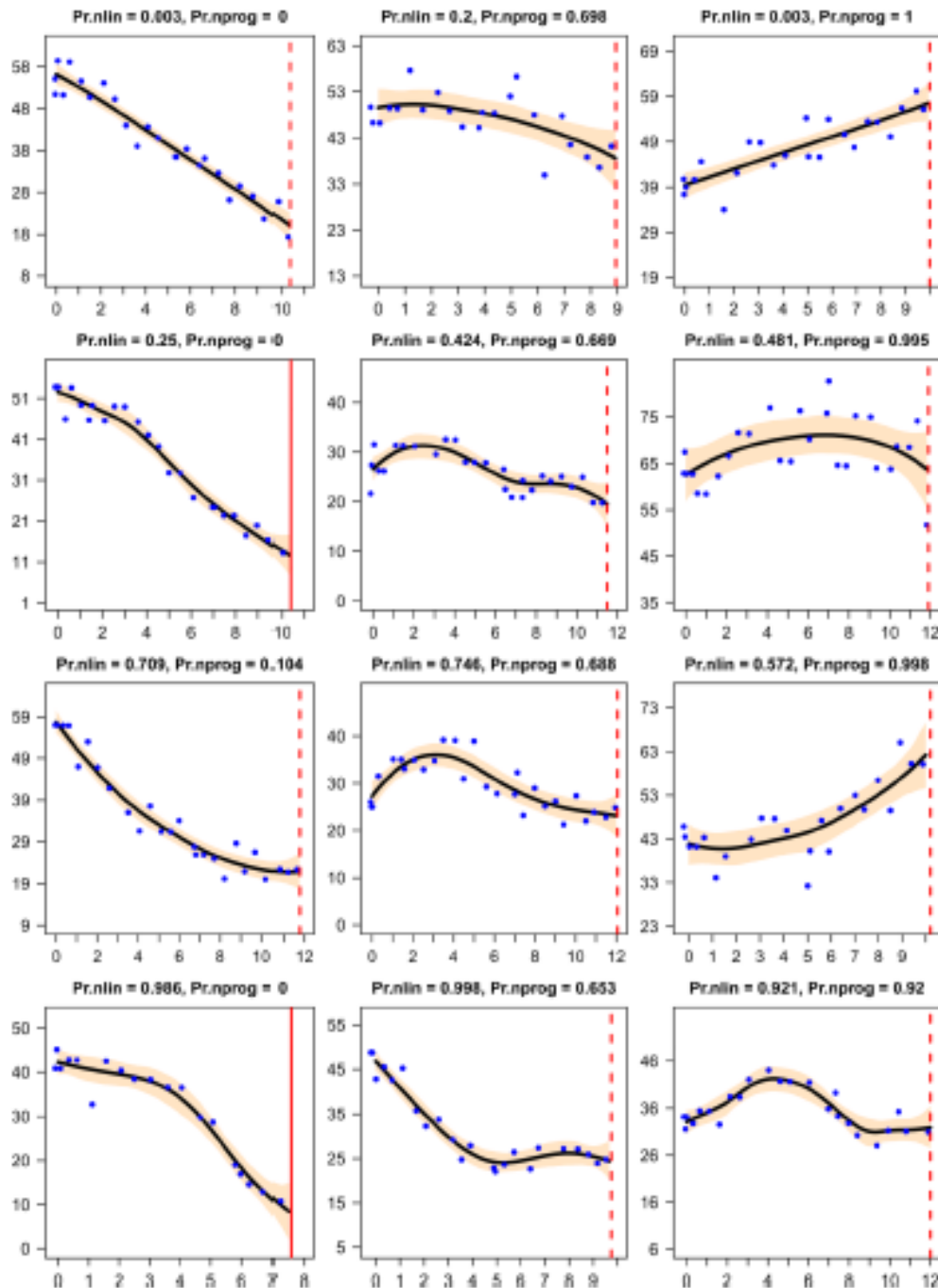
CKD Progression

Definition of Progression

- In population-based cohorts with healthy volunteers, “normal” GFR decline is 0.2-1ml/min/1.73m²/year
- No clear definition of progression and rapid progression
- Suggested definitions (KDIGO 2012):

Category	Definition
Progression	Decline in eGFR Category
Certain progression	Decline in eGFR category + 25% reduction in GFR
Rapid Progression	>5 ml/min/1.73m ² /year fall in eGFR

Non-Linear Decline in eGFR



- 846 AASK patients with at least 3 years follow up and 8 GFR measurements
- 42% had either a non-linear trajectory or a prolonged period of non-progression
- Predictors of a non-progression period included GFR > 40 at baseline and the absence of proteinuria
- 9% had both a period of non-progression and a period of rapid decline

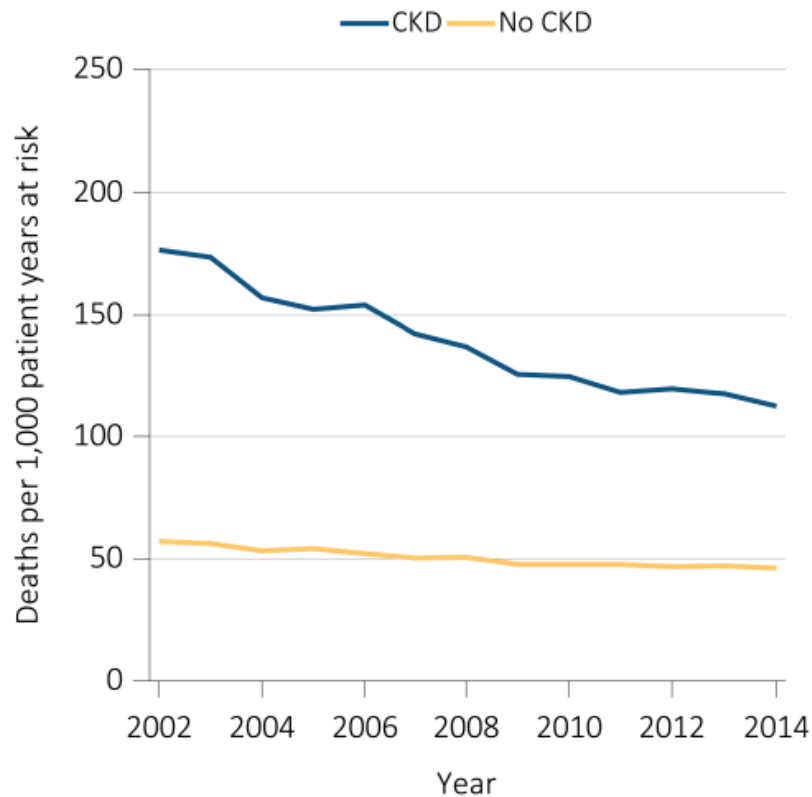
CKD Progression and Risk of All-cause mortality and ESRD

Definition of progression	All-cause mortality HR** (95% CI)	ESRD* HR** (95% CI)
Certain rise	1.51 (1.46–1.56)	0.33 (0.26–0.42)
Uncertain rise	1.12 (1.08–1.16)	0.39 (0.30–0.51)
Stable (reference)	Ref	Ref
Uncertain drop	0.98 (0.95–1.01)	2.13 (1.84–2.47)
Certain drop	1.89 (1.83–1.95)	5.11 (4.56–5.71)

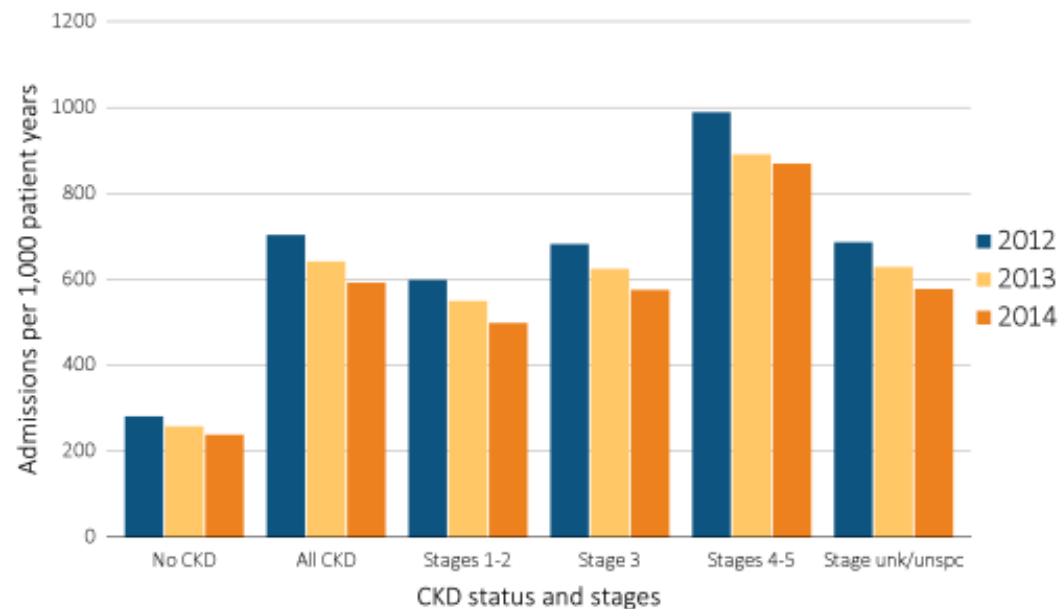
- ~600,000 adults with at least two outpatient creatinine measures spaced 6 months apart.
- Certain change = change in GFR category + 25% change in eGFR.
- Increased risk of mortality and ESRD with progression

Improving outcomes for patients with CKD

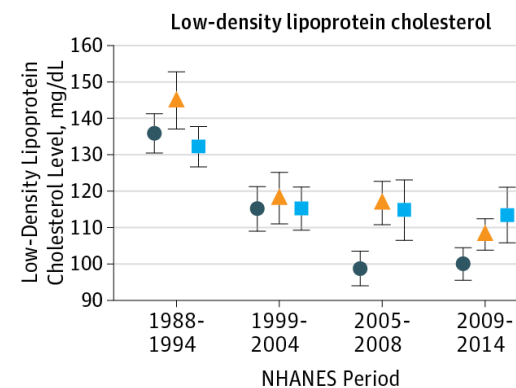
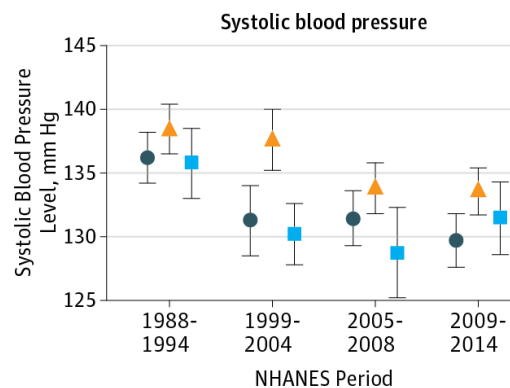
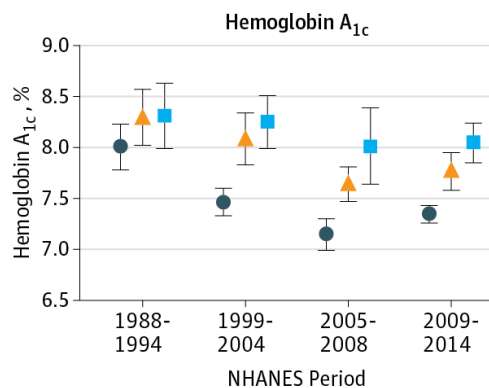
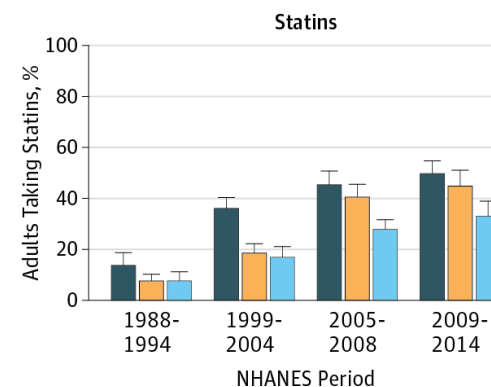
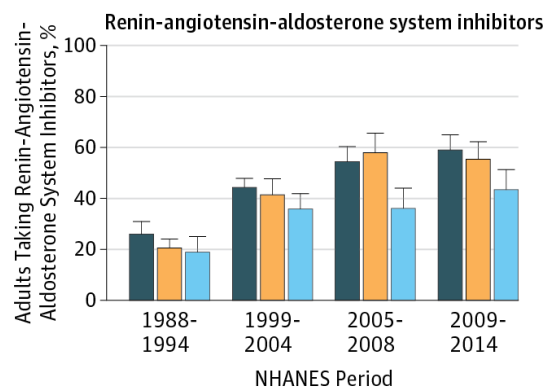
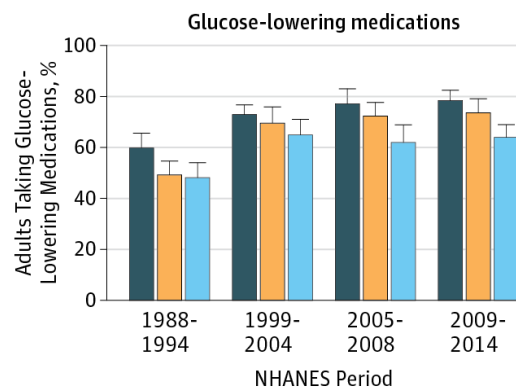
Mortality Rates



Hospital Readmission Rates



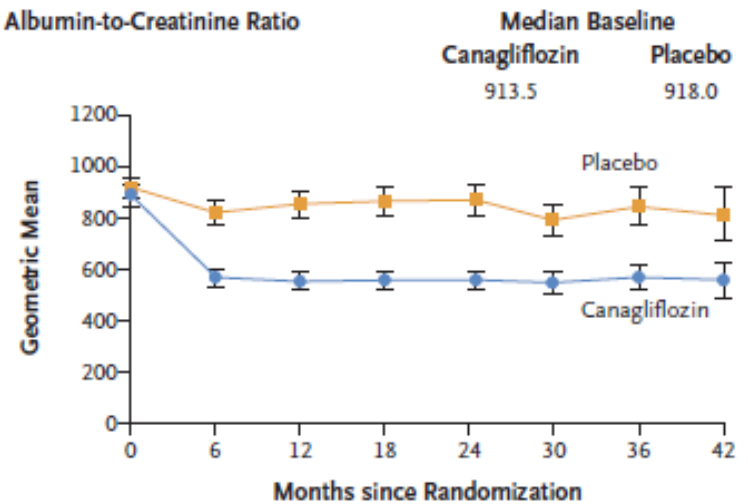
Change in diabetes care over time



Credence

- Trial stopped early due to a 30% reduction in the primary outcome (ESRD or doubling of creatinine) after only 2.5 years

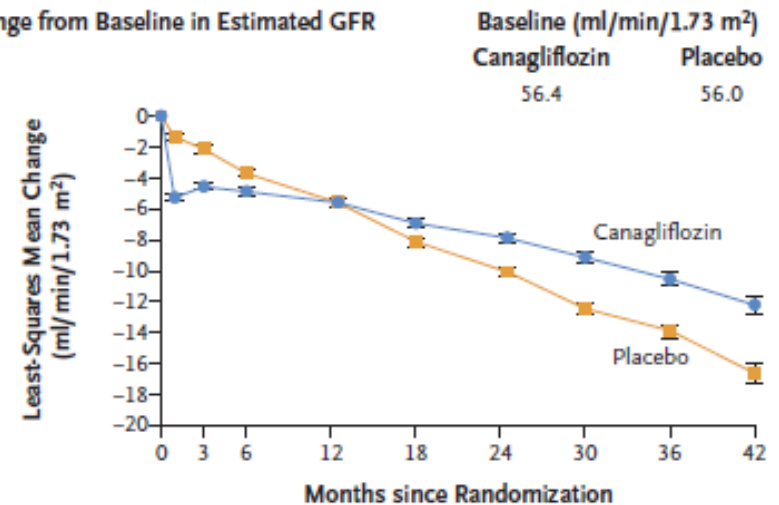
A Urinary Albumin-to-Creatinine Ratio



No. of Patients

Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

B Change from Baseline in Estimated GFR



No. of Patients

Placebo	2178	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2005	1919	1782	1648	1116	652	241

DAPA-CKD

- 4200 patients with CKD stage 2-4 with albuminuria
- Mix of patients with and without T2DM
- Composite endpoint
 - ESRD
 - Cardiovascular or renal death
 - 50% reduction in GFR
- Study stopped early for overwhelming evidence of efficacy

Conclusion

- Early CKD is important and is associated with adverse outcomes including cardiovascular disease
- Delaying progression of CKD is hard as it is likely that significant structural changes have already occurred by the time the GFR has fallen
- Early intervention is likely more effective.
- We have more options for CKD complication delay now than ever before:
 - Bicarbonate
 - SGLT2i
 - ACE/ARB/MRA
 - BP/DM Control

References

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