Brigham and Women's Hospital
Founding Member, Mass General Brigham

CKD Epidemiology

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CONTINUING MEDICAL EDUCATION
DEPARTMENT OF MEDICINE

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

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Residency @ Beaumont Hospital, Dublin
Renal Fellowship @ BWH
Research Fellowships @ BCH and FHS
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Clinical Focus

- Lupus Nephritis
- ICU Nephrology

Disclosure

- Consultant for GlaxoSmithKline, Apellis Pharma, Optum Consulting
- 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. Cockroft-Gault
B. MDRD
C. CKD-EPI Cystatin-C
D. CKD-EPI Creatinine
E. CKD-EPI Creatinine-Cystatin C

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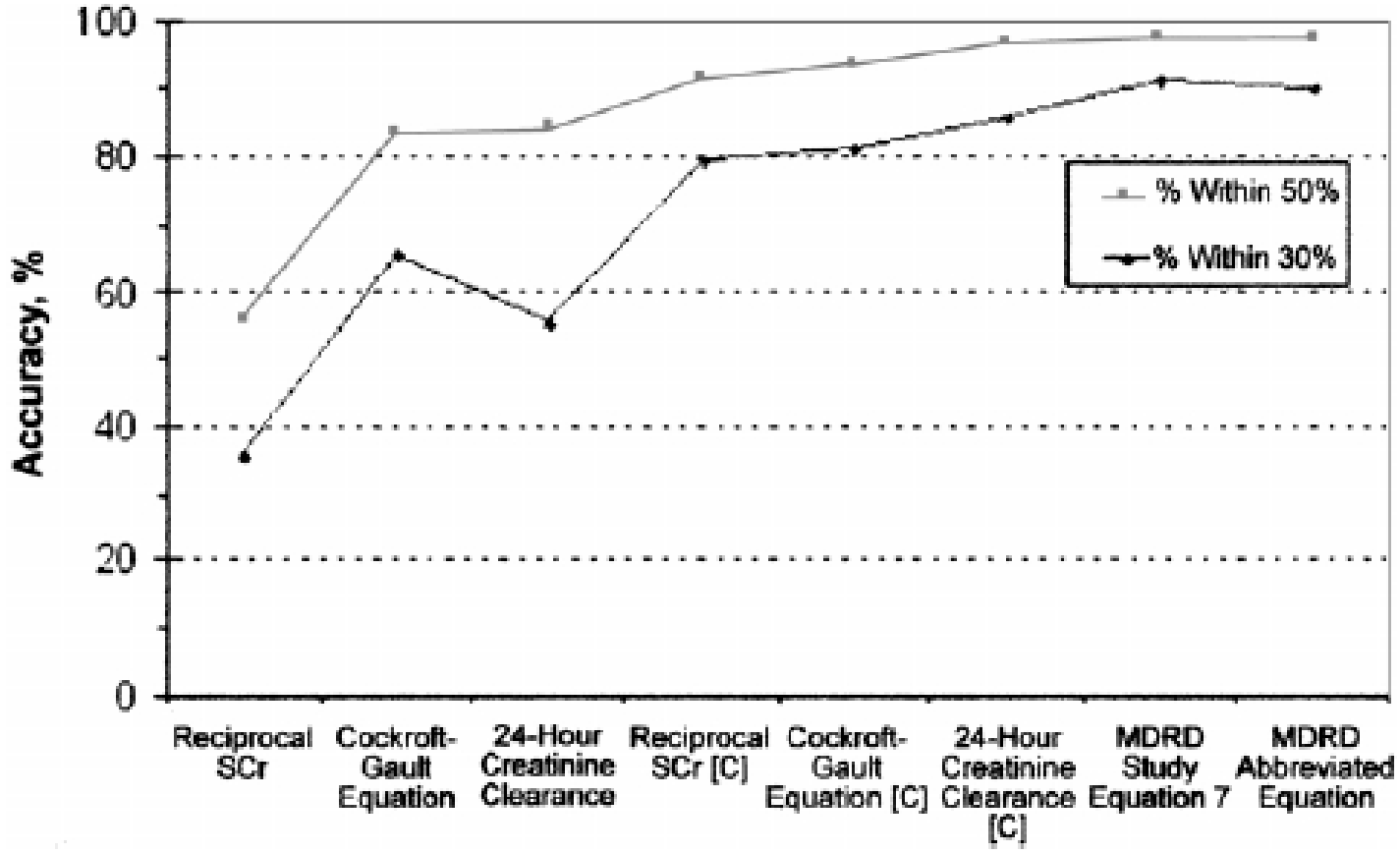
E. CKD-EPI Creatinine-Cystatin C

How do we measure kidney function?

GFR Measurement and Estimation

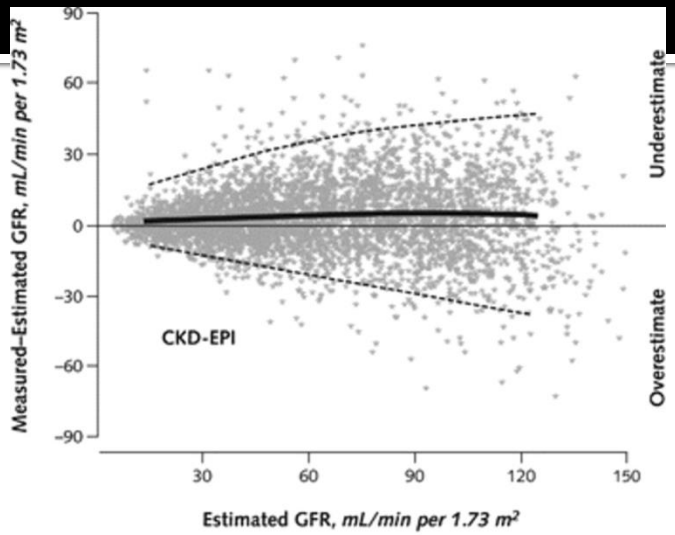
Method	Description	Advantages	Potential Limitations
Measured GFR	•Urinary clearance of an exogenous or endogenous filtration marker. •Plasma clearance of an exogenous filtration marker.	•Accurate (gold standard methods)	•Inconvenient to patients •Expensive •Not suitable for population-based screening
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)

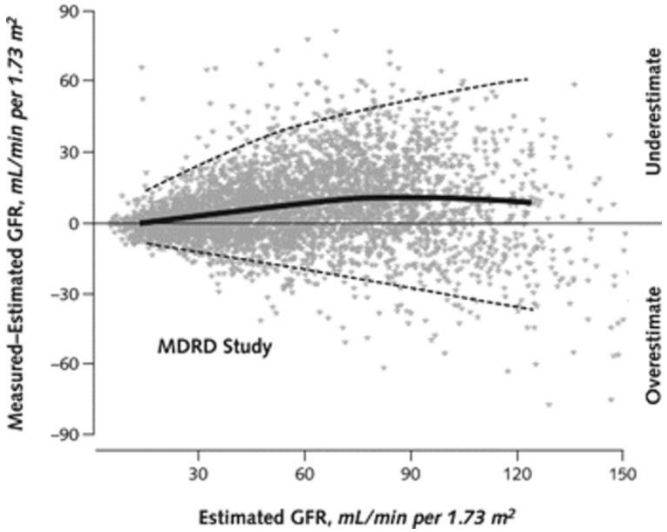
Accuracy of Commonly Used Methods for Estimating GFR



KDOQI Guidelines *AJKD 2002*

CKD-Epi Equation



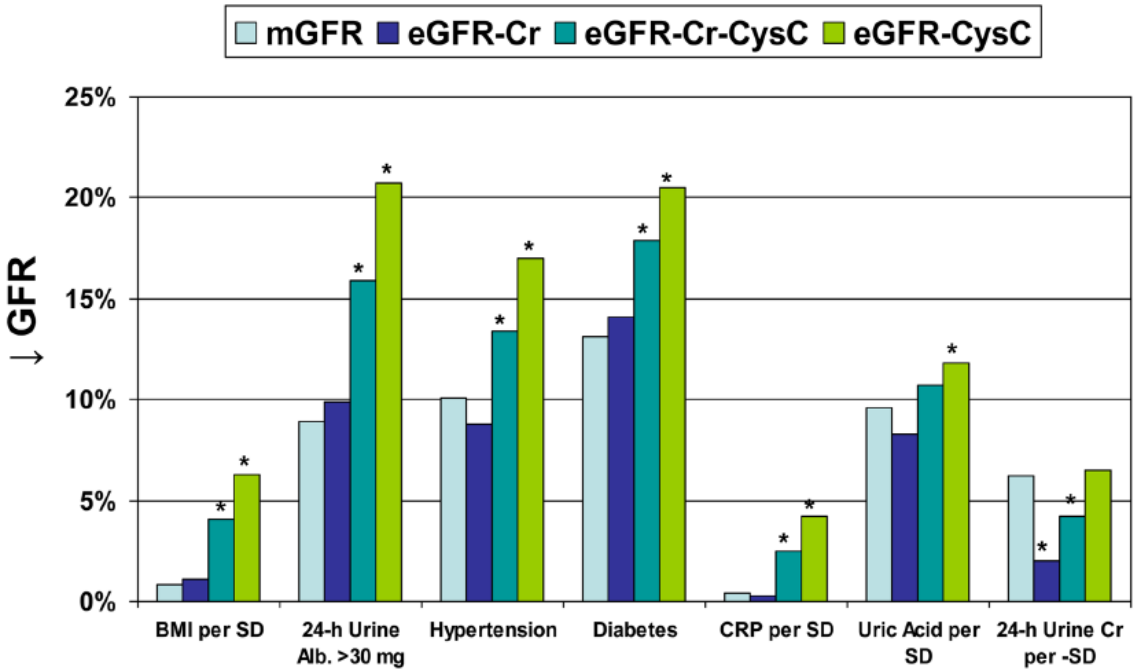


- KDIGO recommends using the CKD-Epi equation in clinical practice and for research.
- Compared to MDRD
  - Less Bias
  - More accurate
  - Improved risk reclassification
- Approximately 84% of measurements within 30% of the true (measured GFR)

Levey et al, *Annals Int Med 2009*

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 eGFRcr was o.6ml/min
- Wide range of values for individuals at a given eGFR
- No improvement with eGFRcys
- Likely should be reported as a range rather than a single number

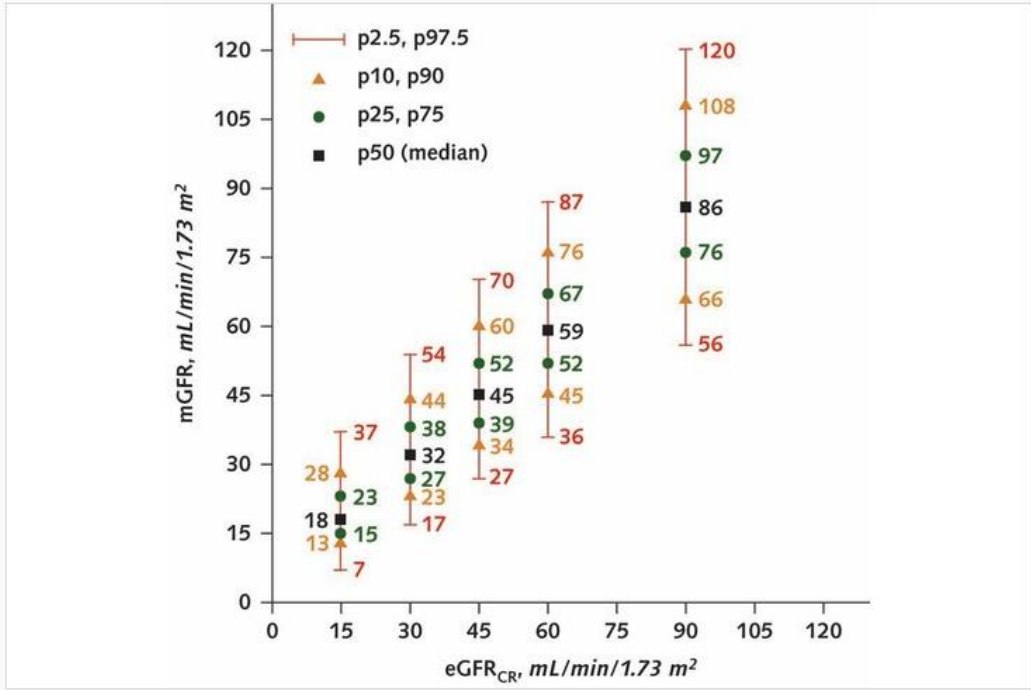


Figure 1. Distribution of mGFR at selected eGFR$_{CR}$ thresholds in 3223 participants of 4 cohort studies.

Shafi et al, Ann Int Med 2022

Should we adjust for race when calculating eGFR?

VIEWPOINT

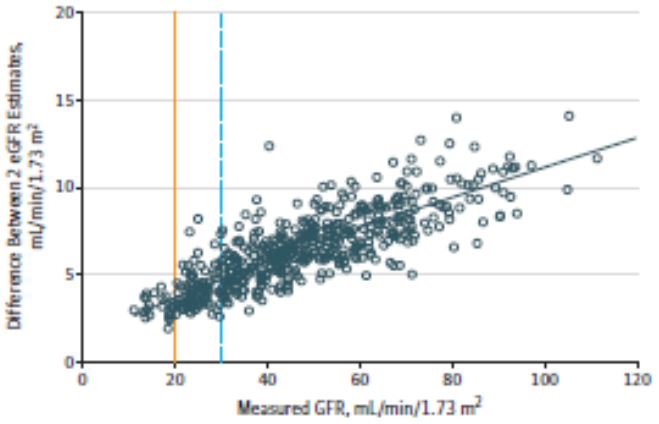
Reconsidering the Consequences of Using Race to Estimate Kidney Function

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



Eneanya et al, *JAMA 2020*

Should we adjust for race when calculating eGFR?

The NEW ENGLAND JOURNAL of MEDICINE

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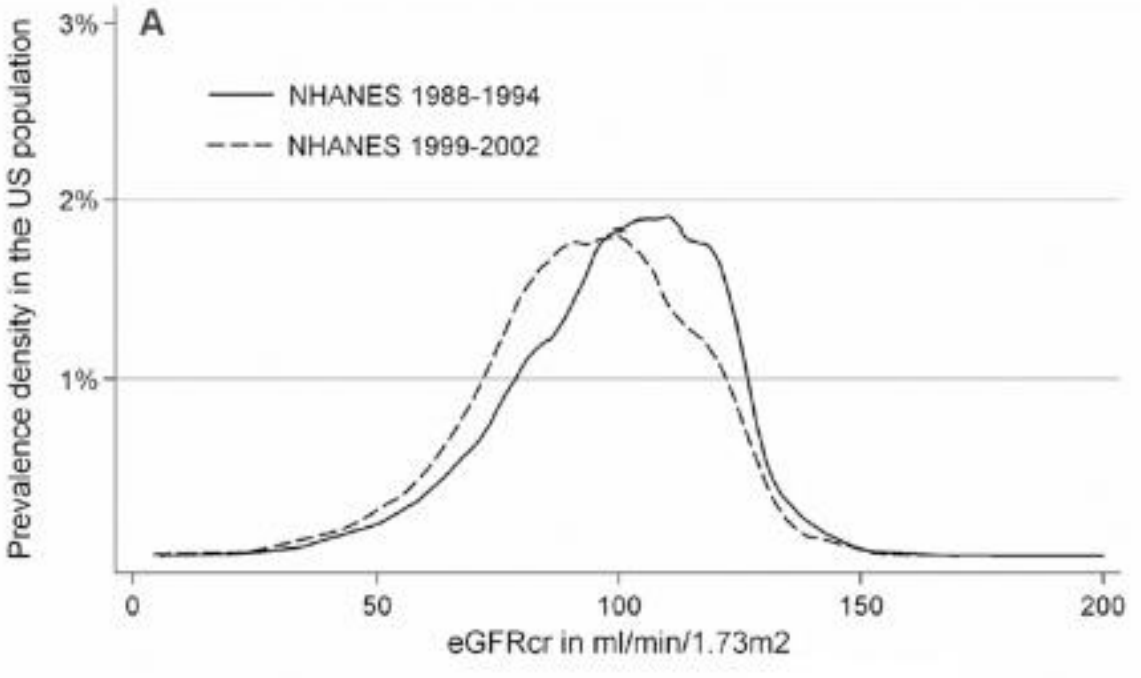
New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race

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*

Inker et al, NEJM 2021

How common is CKD?

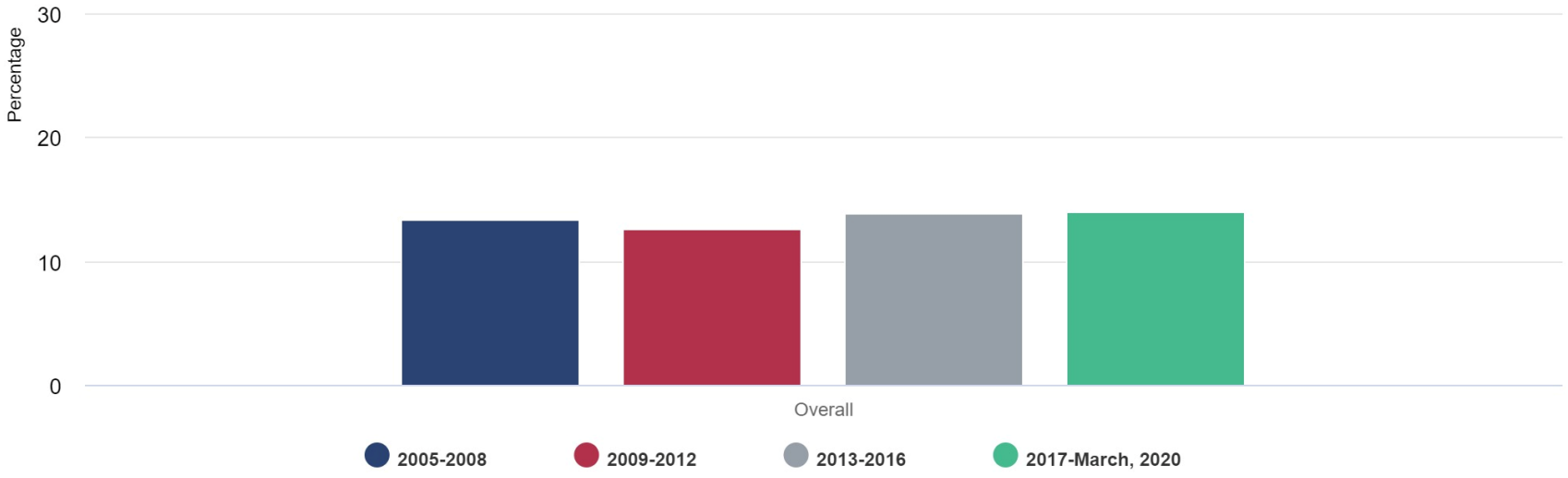
Prevalence of CKD



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

Grams et al, *AJKD 2013*

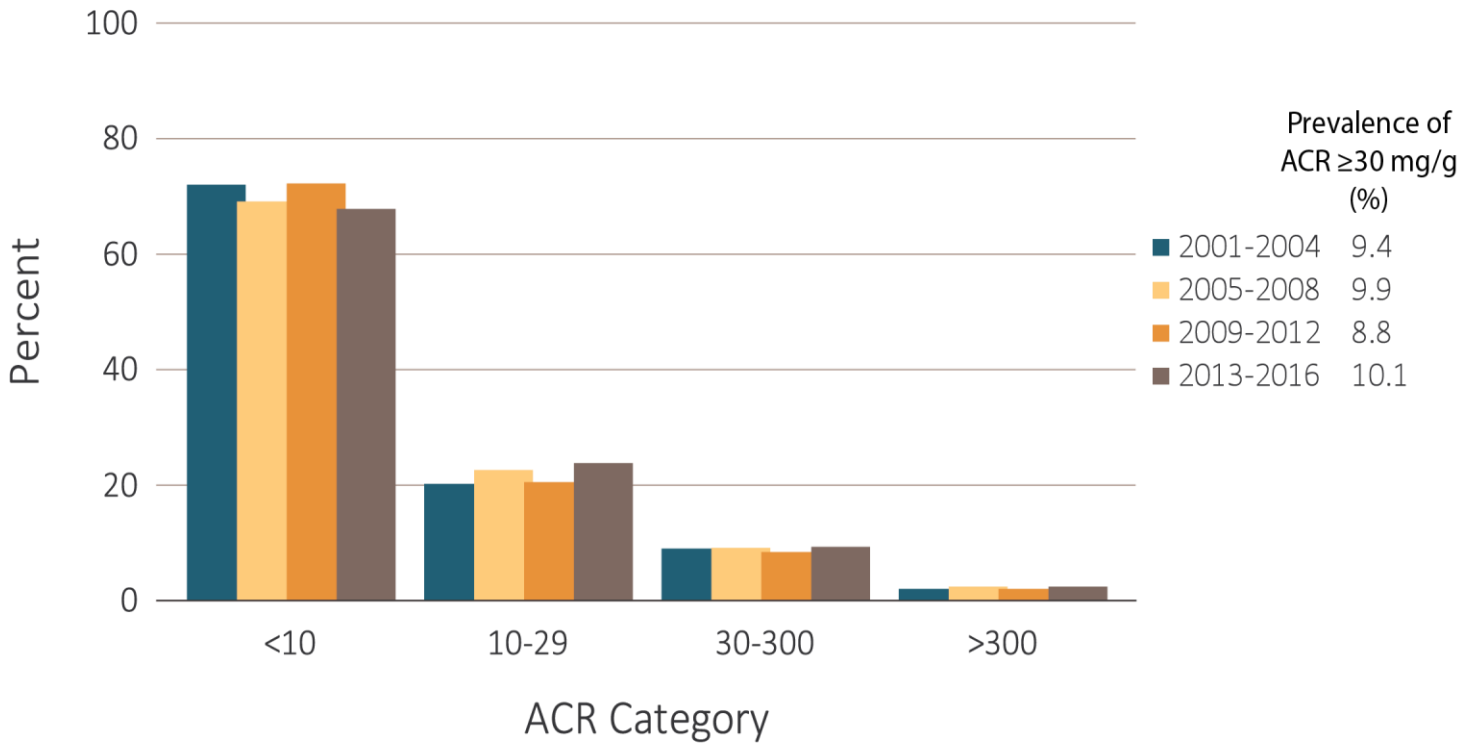
Prevalence of CKD in US Adults



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

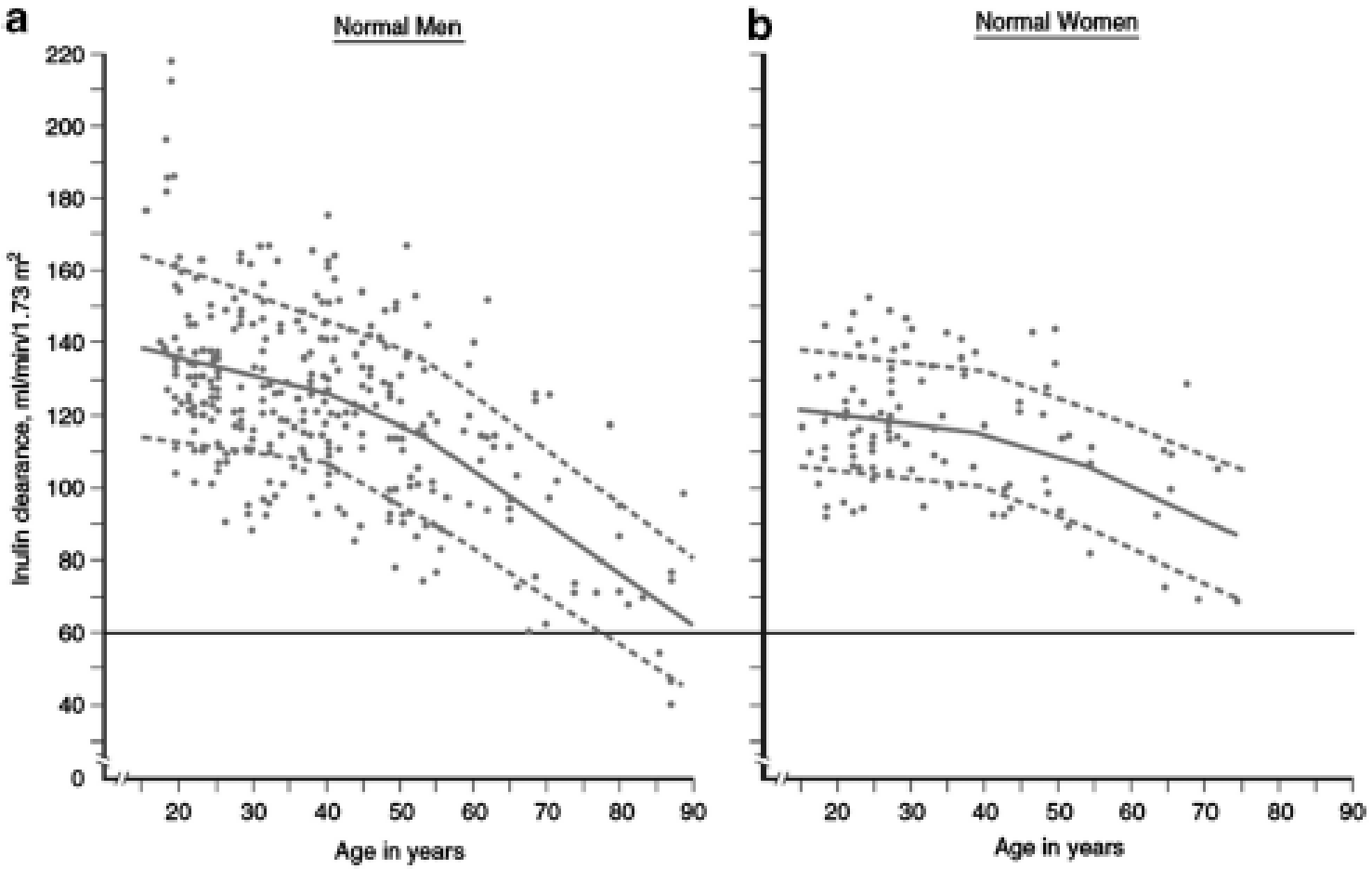
USRDS Annual Report 2024

Prevalence of albuminuria



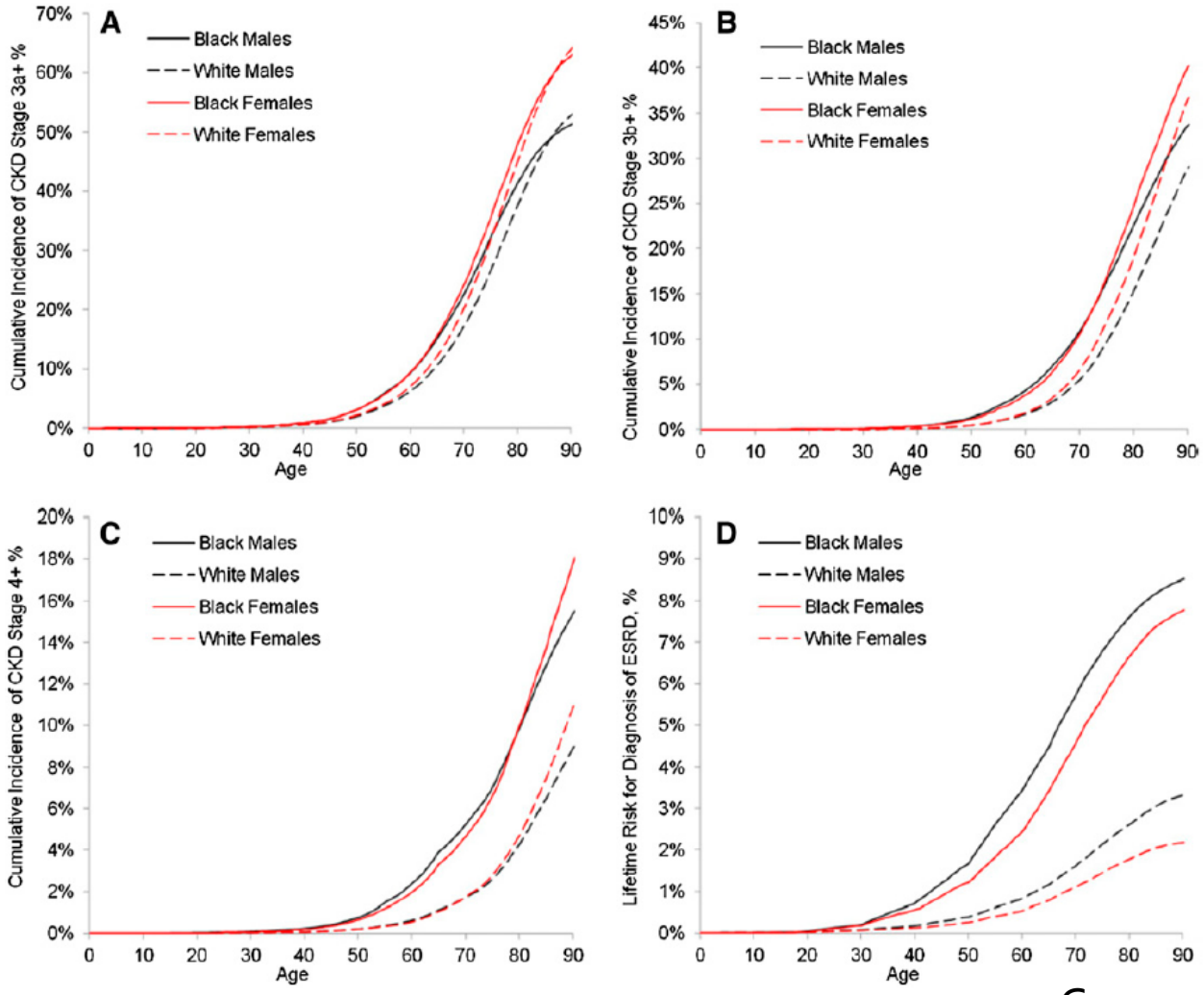
Annual Report, *USRDS 2018*

Increasing Prevalence of CKD with Age



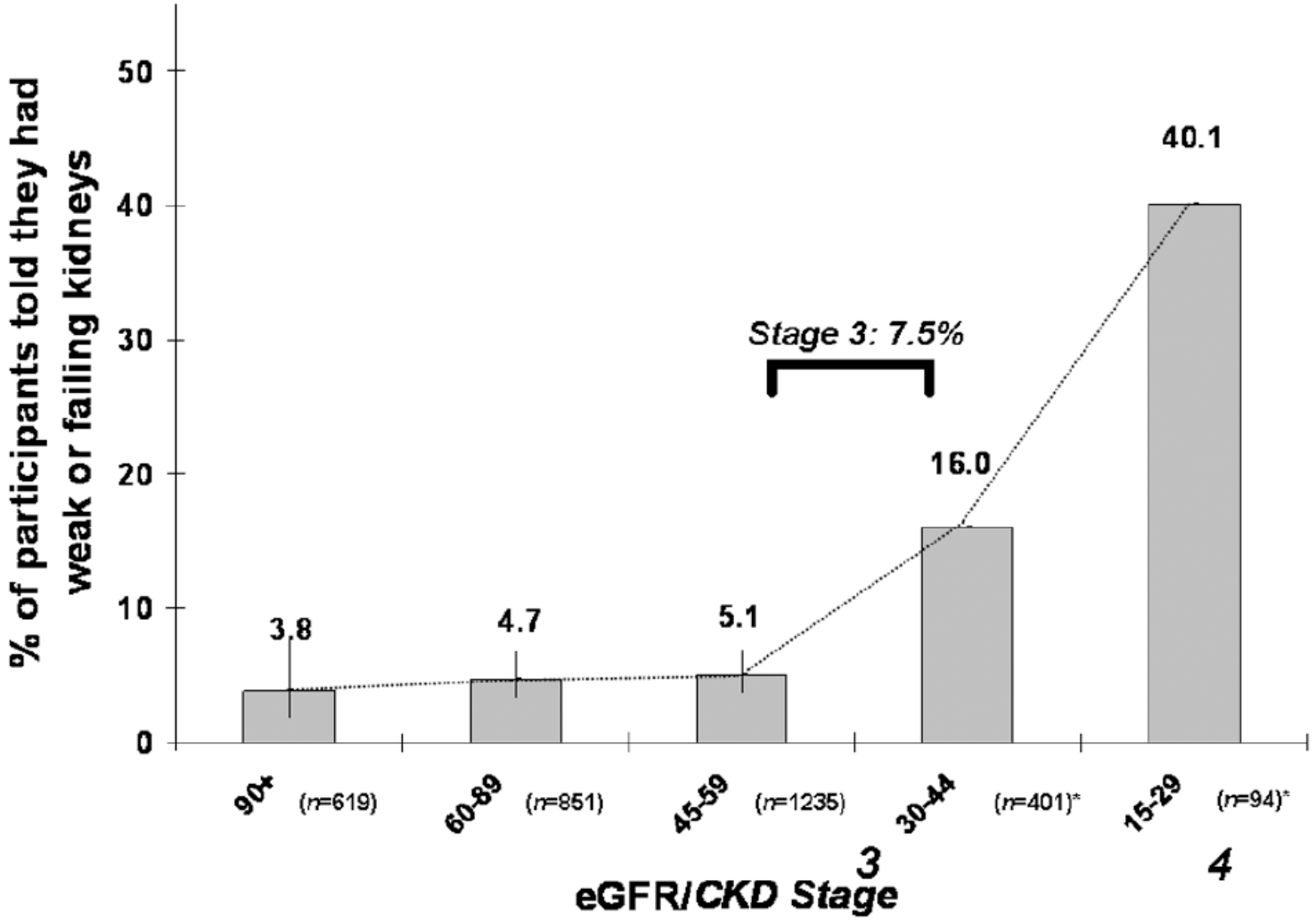
Wesson et al, *Physiology of the Human Kidney 1969*

Lifetime Risk of CKD



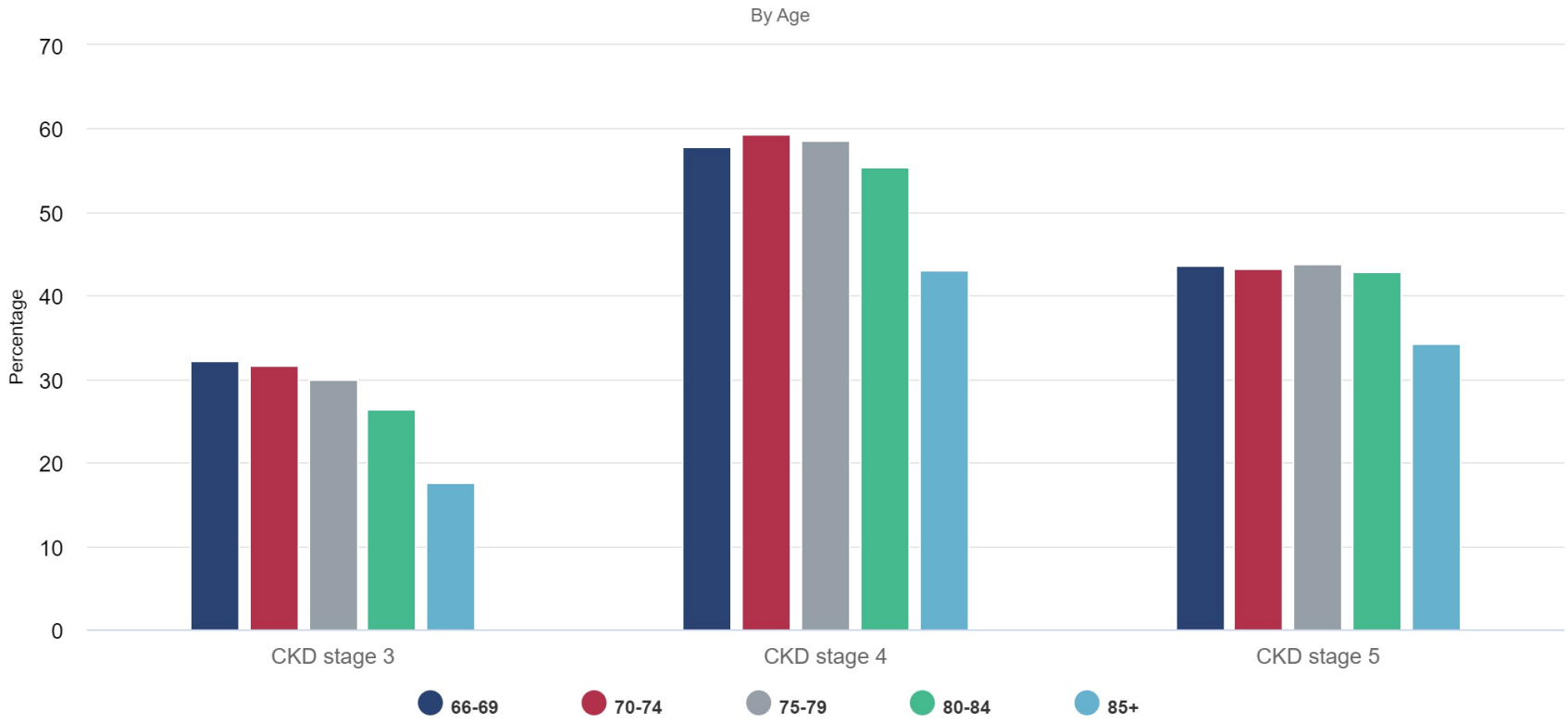
Grams et al, *AJKD 2013*

Poor awareness of CKD



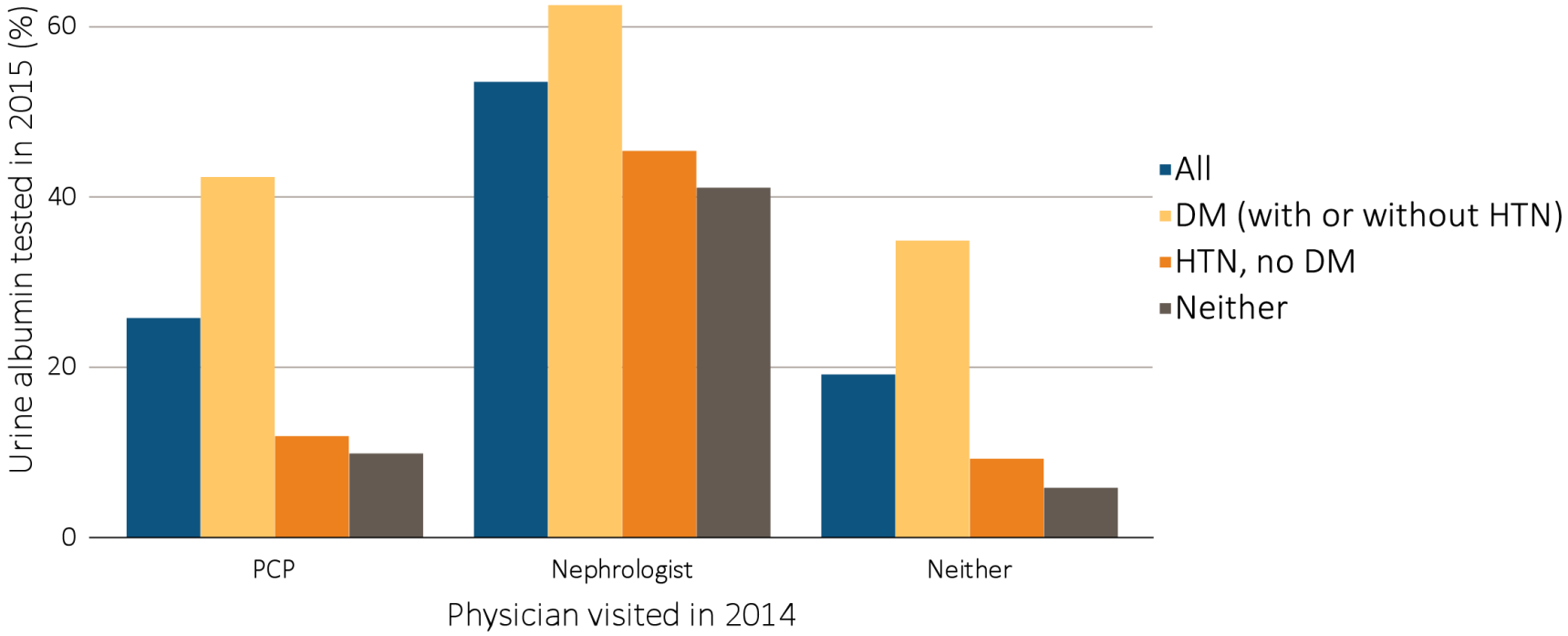
Plantinga et al, *Adv Chr Kid Dis 2013*

Low referral rates to nephrology particularly in the elderly



USRDS Annual Report 2022

Poor awareness of CKD among physicians



USRDS Annual Report 2018

Is early CKD important?

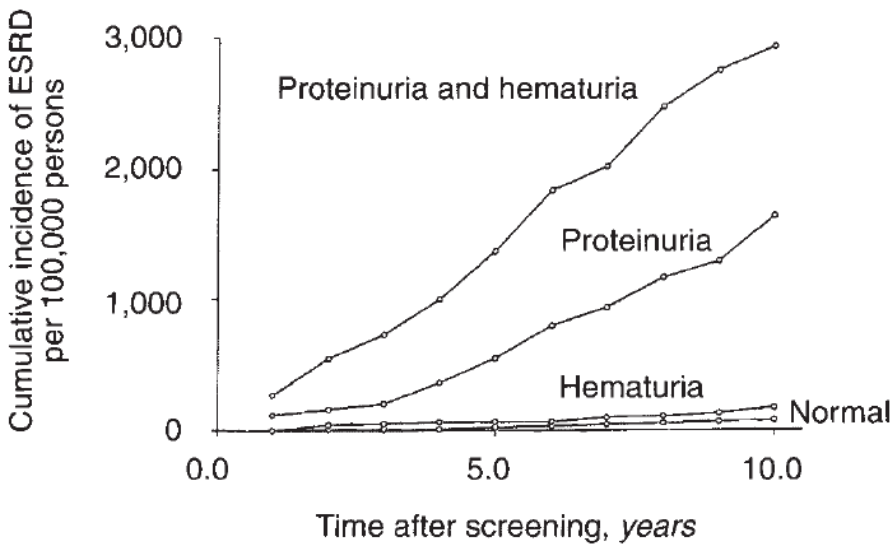
Asymptomatic Hematuria and the Risk of ESRD

- 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)

Vivante et al. JAMA 2011. 306;7: 729

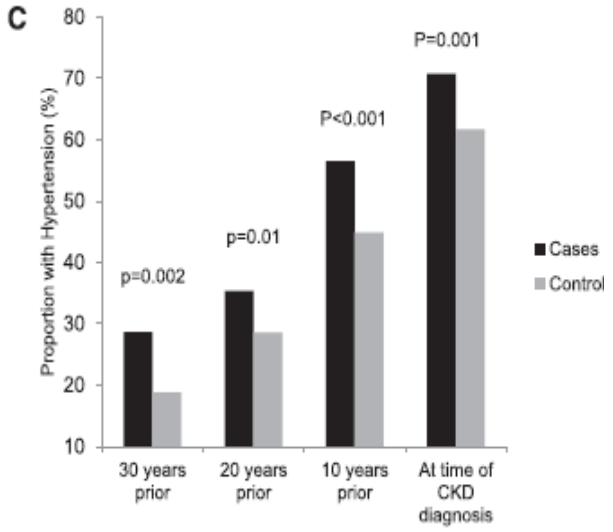
Risk of developing ESKD in a screening cohort

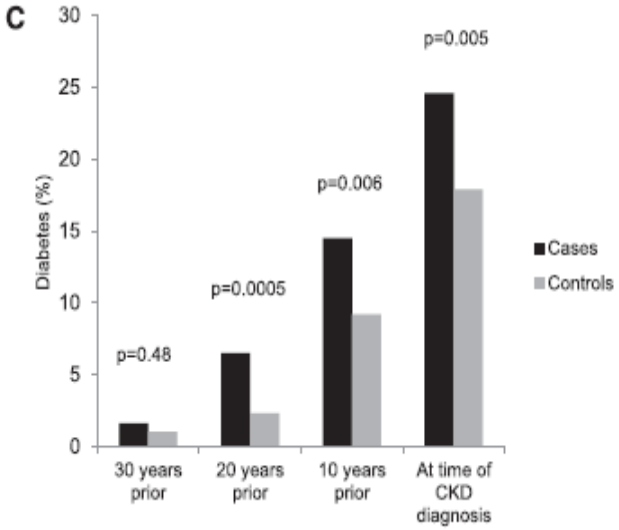
- >107,000 subjects, single dipstick UA & BP check
- 10 year follow up; 193 ESKD patients identified
- Dipstick proteinuria OR: 14.9 (10.9-20.2)
- Hematuria OR: 2.3 (1.62-3.3)
- Male OR: 1.41 (1.04-1.92)
- DBP OR: 1.39 (1.17-1.64) per 10mmHg

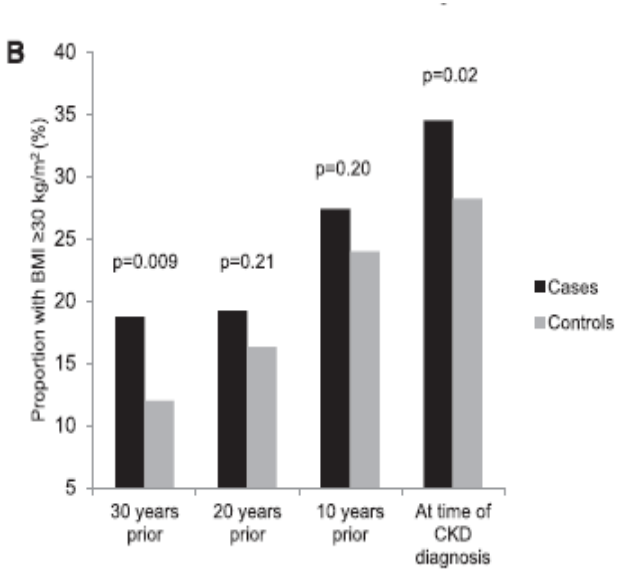


Iseki et al. KI 1996, 49(3): 800

Long-term Risk Factors for CKD

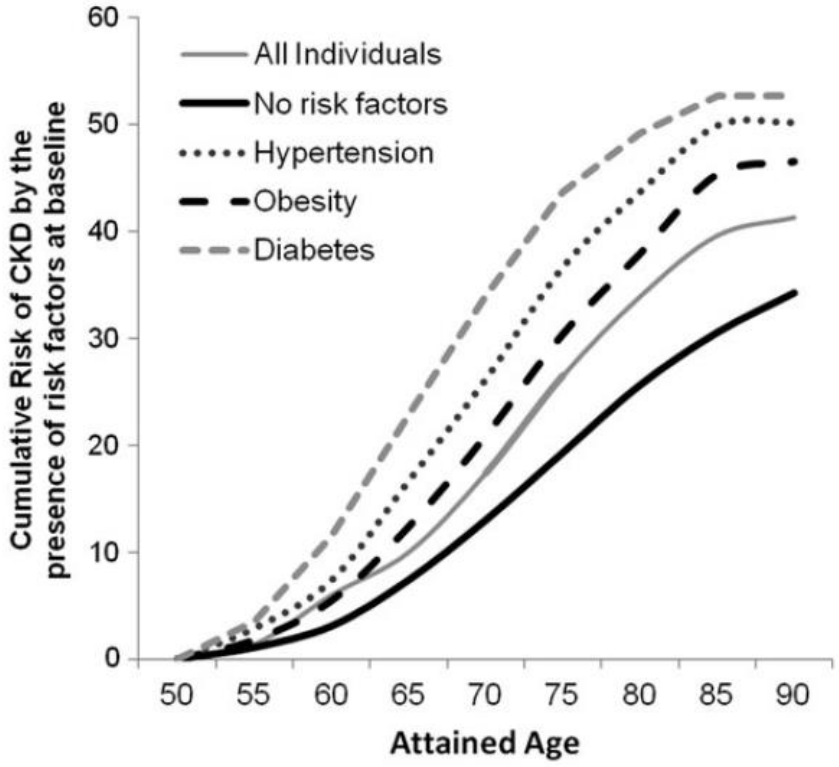


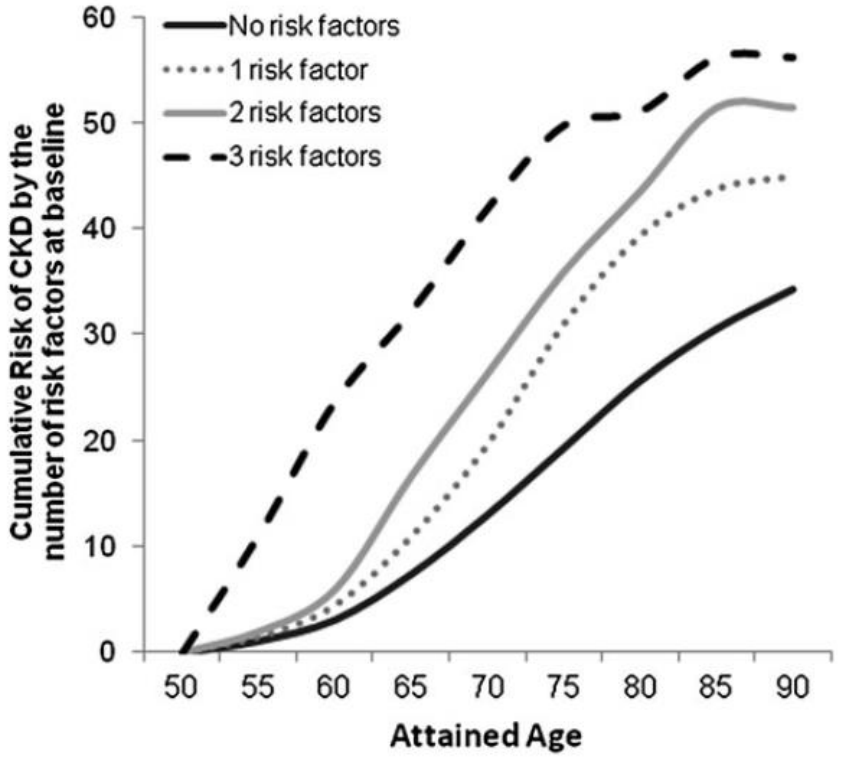




McMahon et al, *JASN 2014*

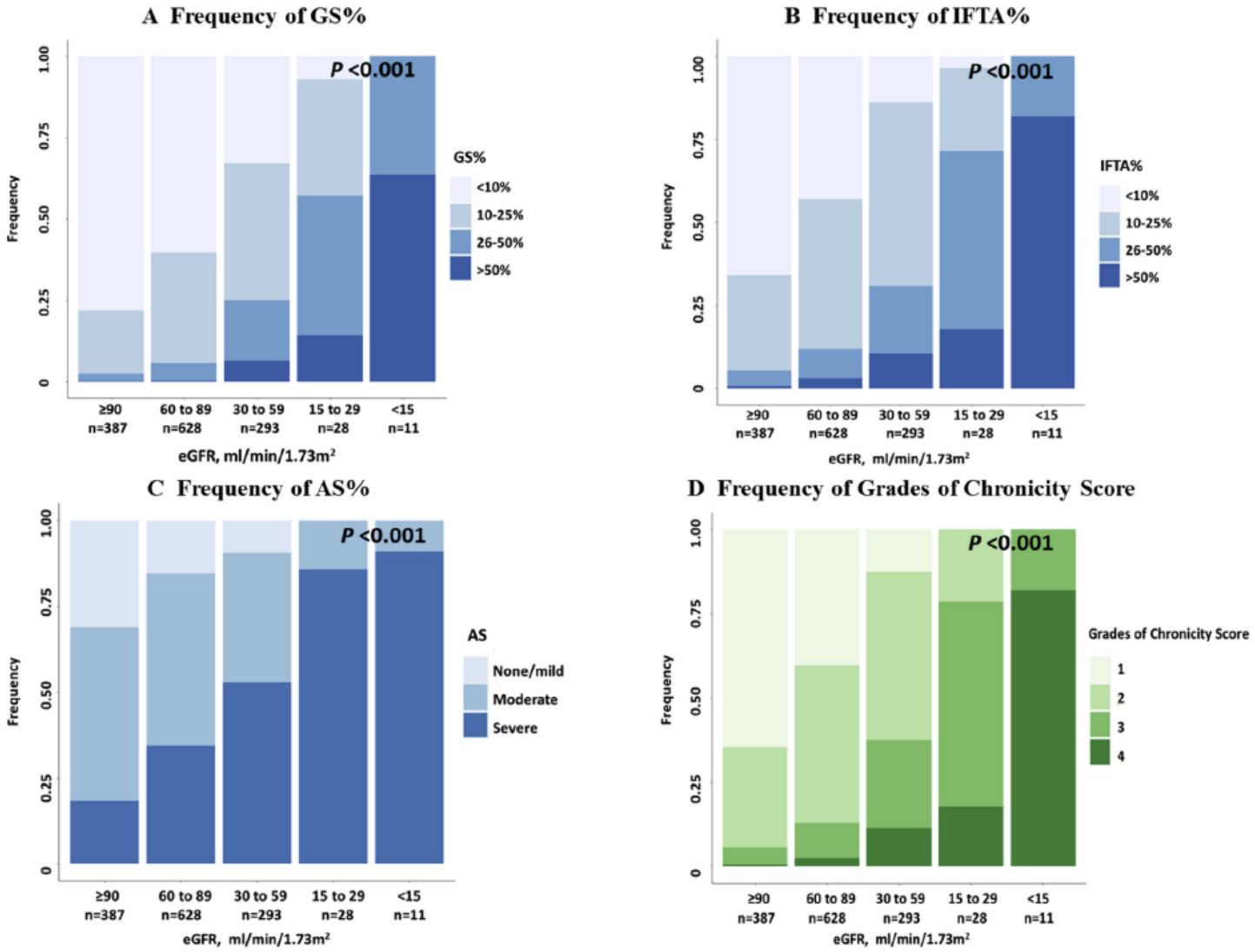
Residual Lifetime Risk of CKD





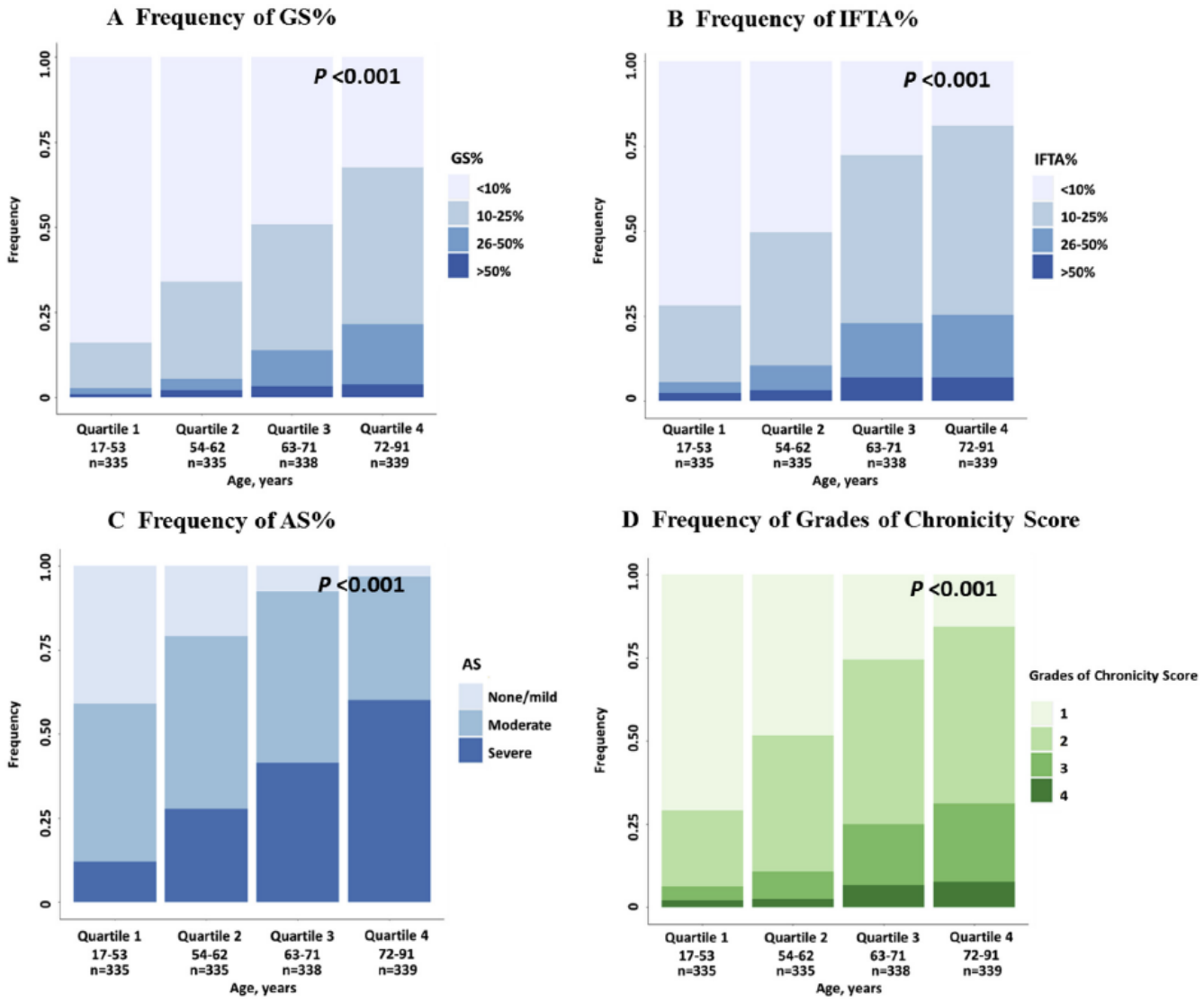
McMahon et al, *NDT 2016*

Distinct pathologic profile in patients with early CKD – GFR categories



Li et al, AJKD 2021

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



Li et al, AJKD 2021

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

KDIGO CKD Guidelines 2012

KIDNEY PRECISION MEDICINE PROJECT

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

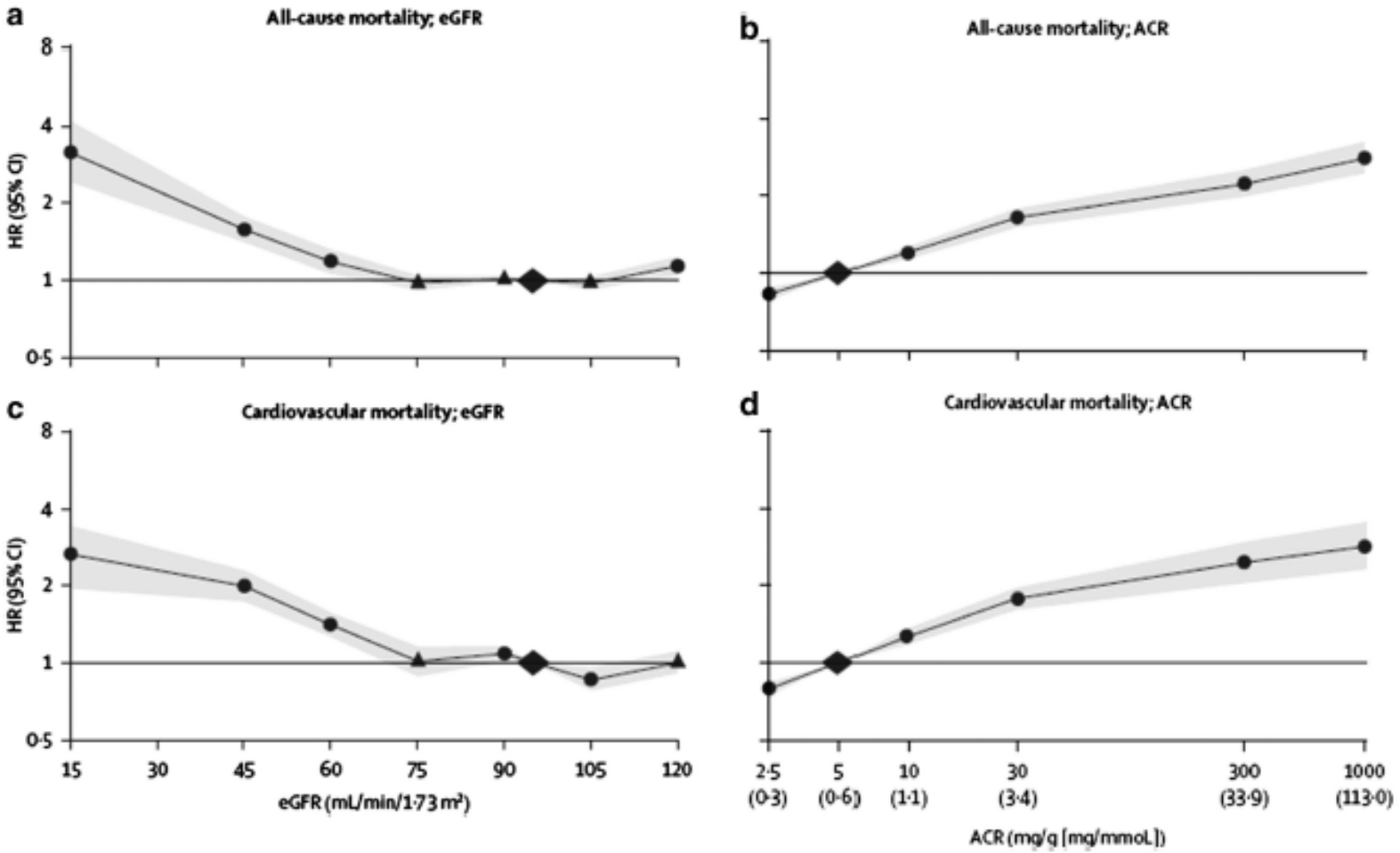
KIDNEY PRECISION MEDICINE PROJECT

- 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.

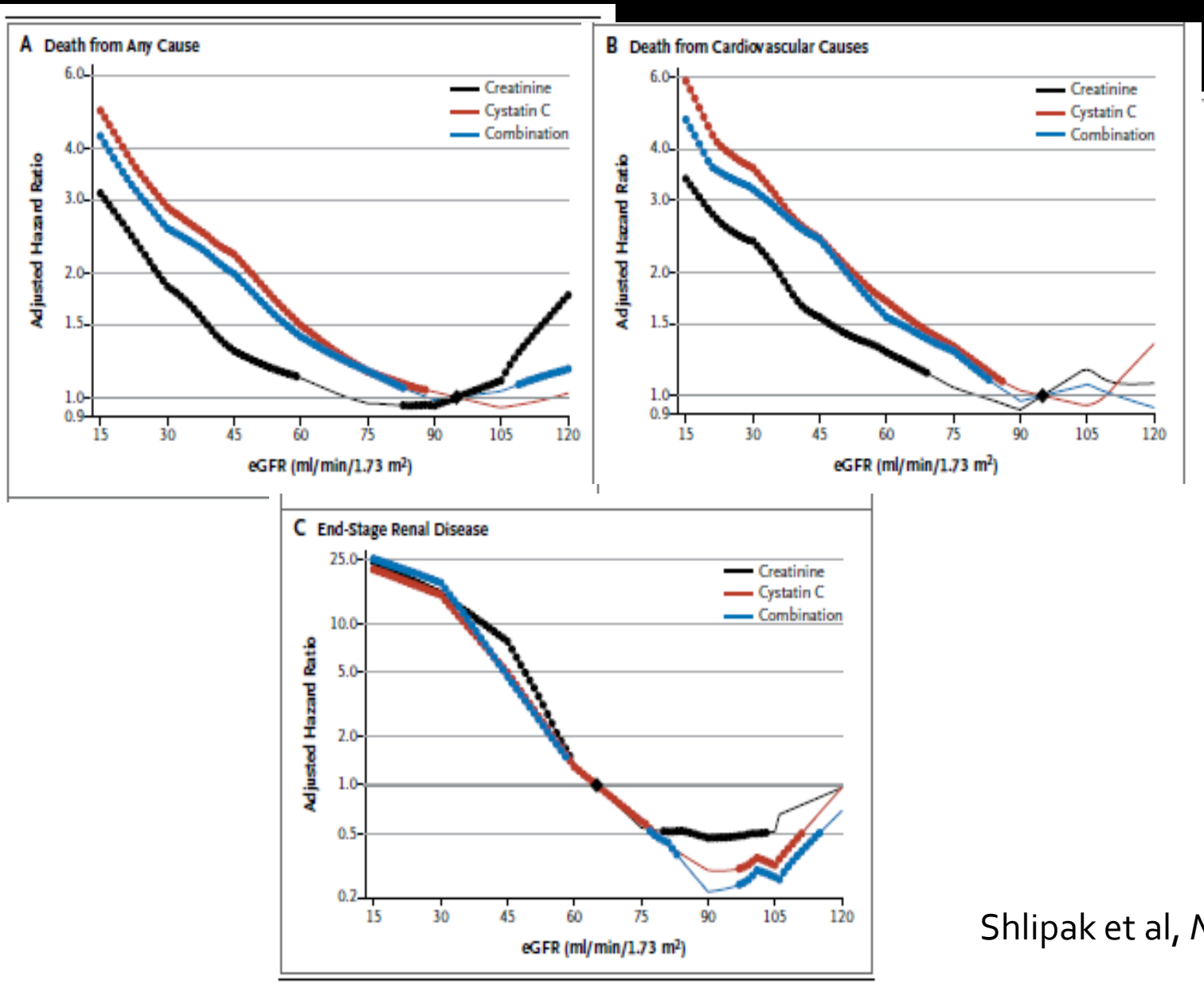
What are the real world consequences of early CKD?

CKD and Cardiovascular Disease



Matsushita et al, *Lancet 2010*

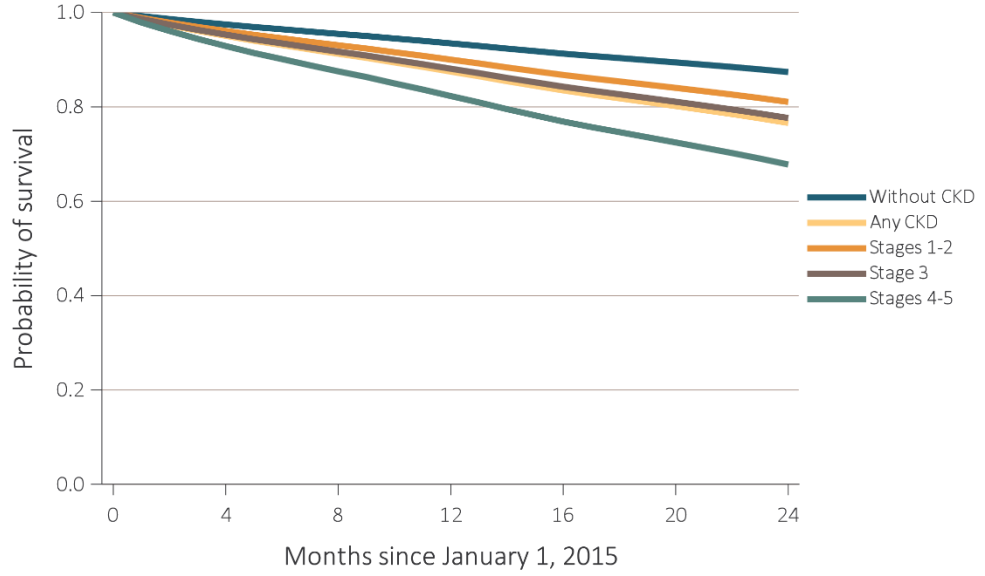
Cystatin C is a better predictor of CVD



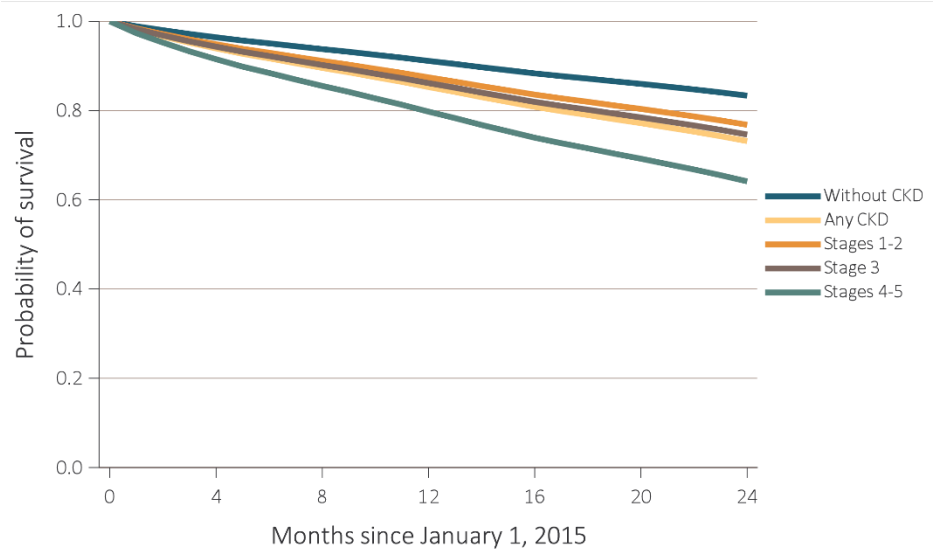
Shlipak et al, *NEJM 2013*

CKD Increases mortality in CVD

Acute MI



CVA/TIA



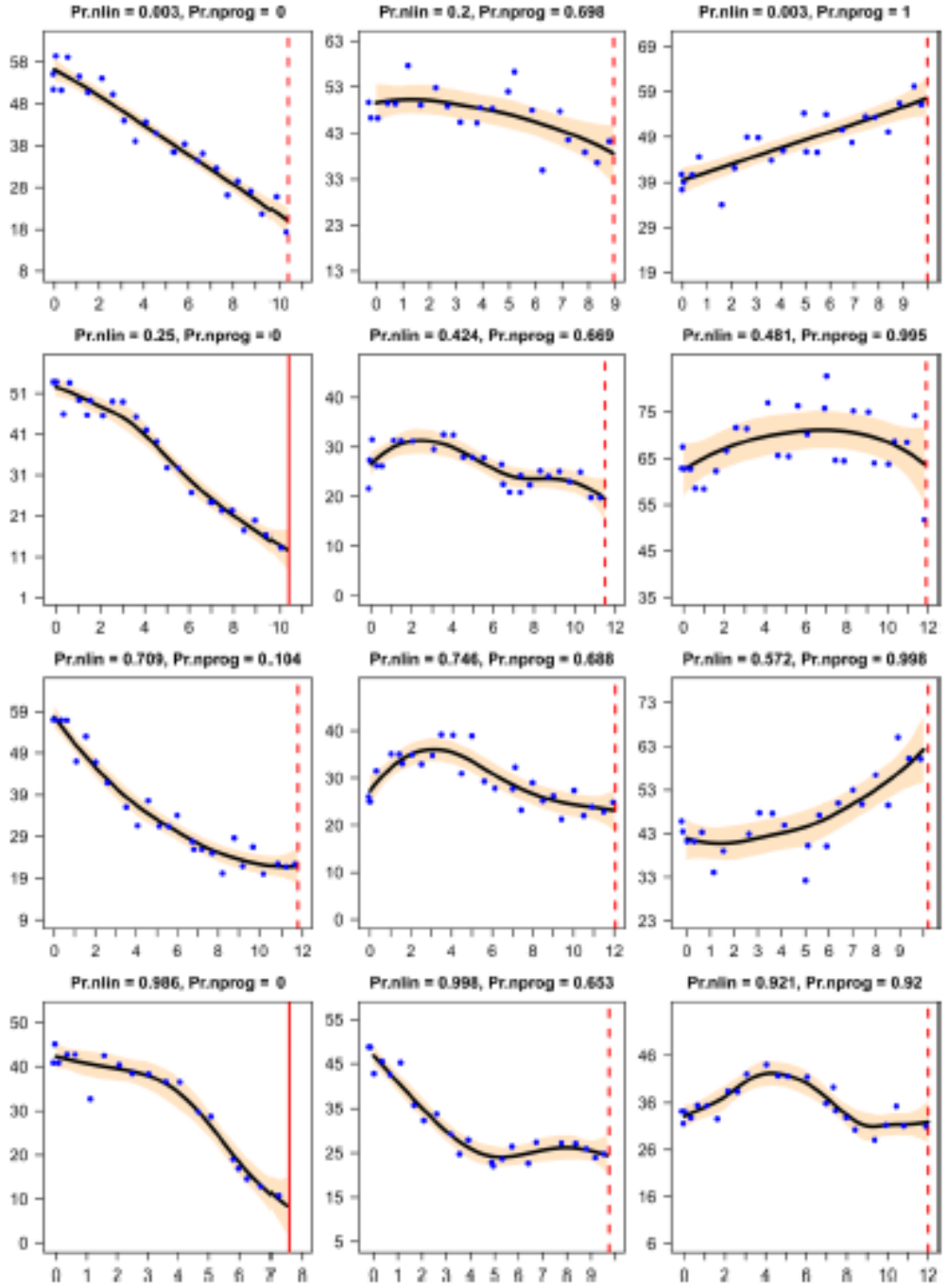
Annual Report, *USRDS 2018*

CKD Progression

Definition of Progression

- In population-based cohorts with healthy volunteers, "normal" GFR decline is 0.2-1ml/min/1.73m^2/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

Li et al, *AJKD 2012*

CKD Progression and Risk of All-cause mortality and ESRD

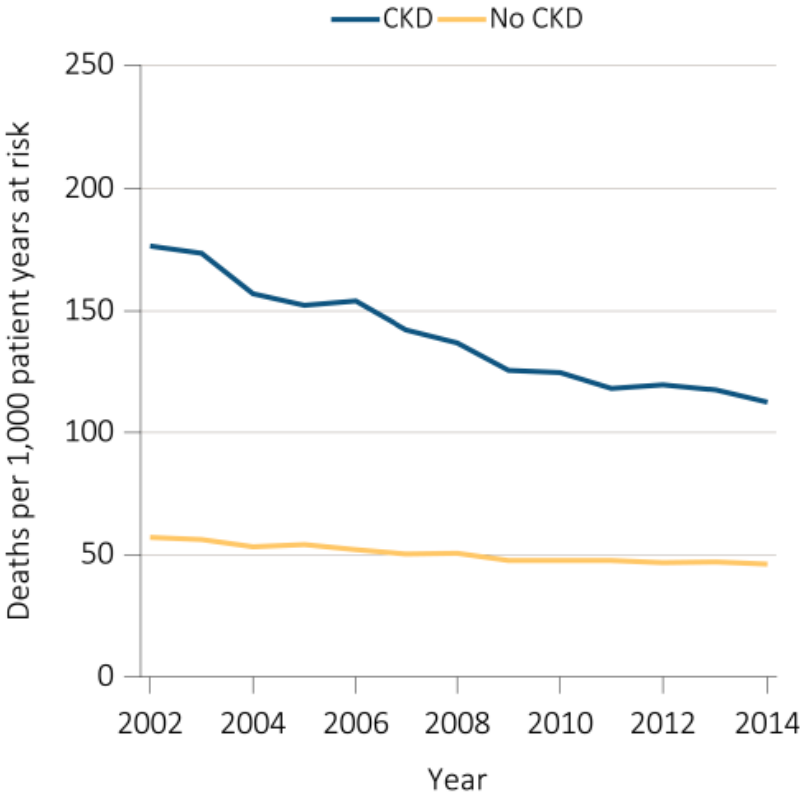
Definition of progression	All-cause mortality HR** (95% CI)	ESRD* HR** (95% CI)
Certain rise	1.51 (1.46–1.56)	0.33 (0.26–0.42)
Uncertain rise	1.12 (1.08–1.16)	0.39 (0.30–0.51)
Stable (reference)	Ref	Ref
Uncertain drop	0.98 (0.95–1.01)	2.13 (1.84–2.47)
Certain drop	1.89 (1.83–1.95)	5.11 (4.56–5.71)

- ~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

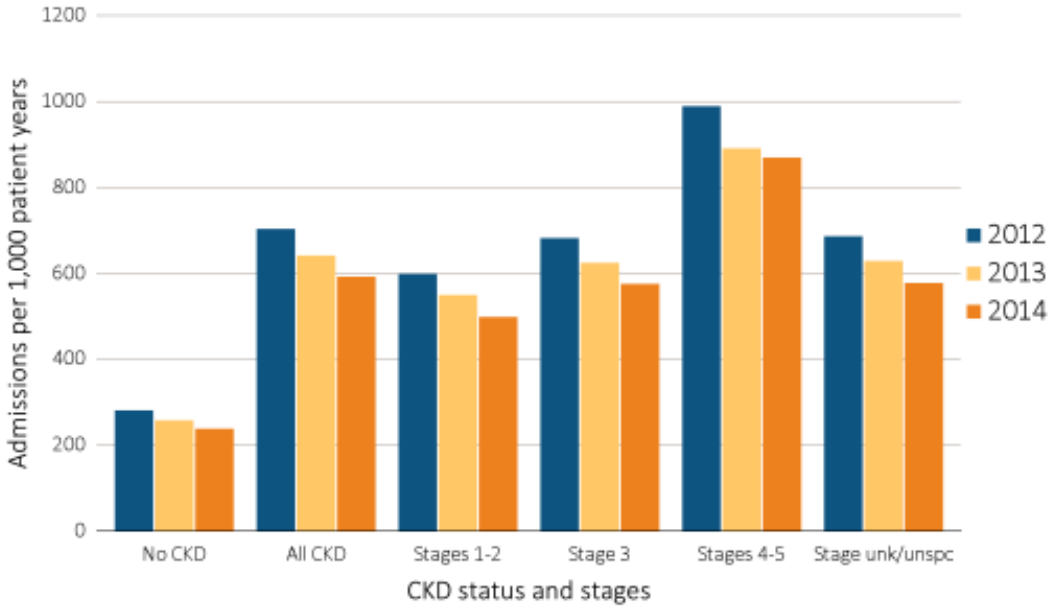
Turin et al, *Am J Nephrol 2012* AND Turin et al, *NDT 2012*

Improving outcomes for patients with CKD

Mortality Rates

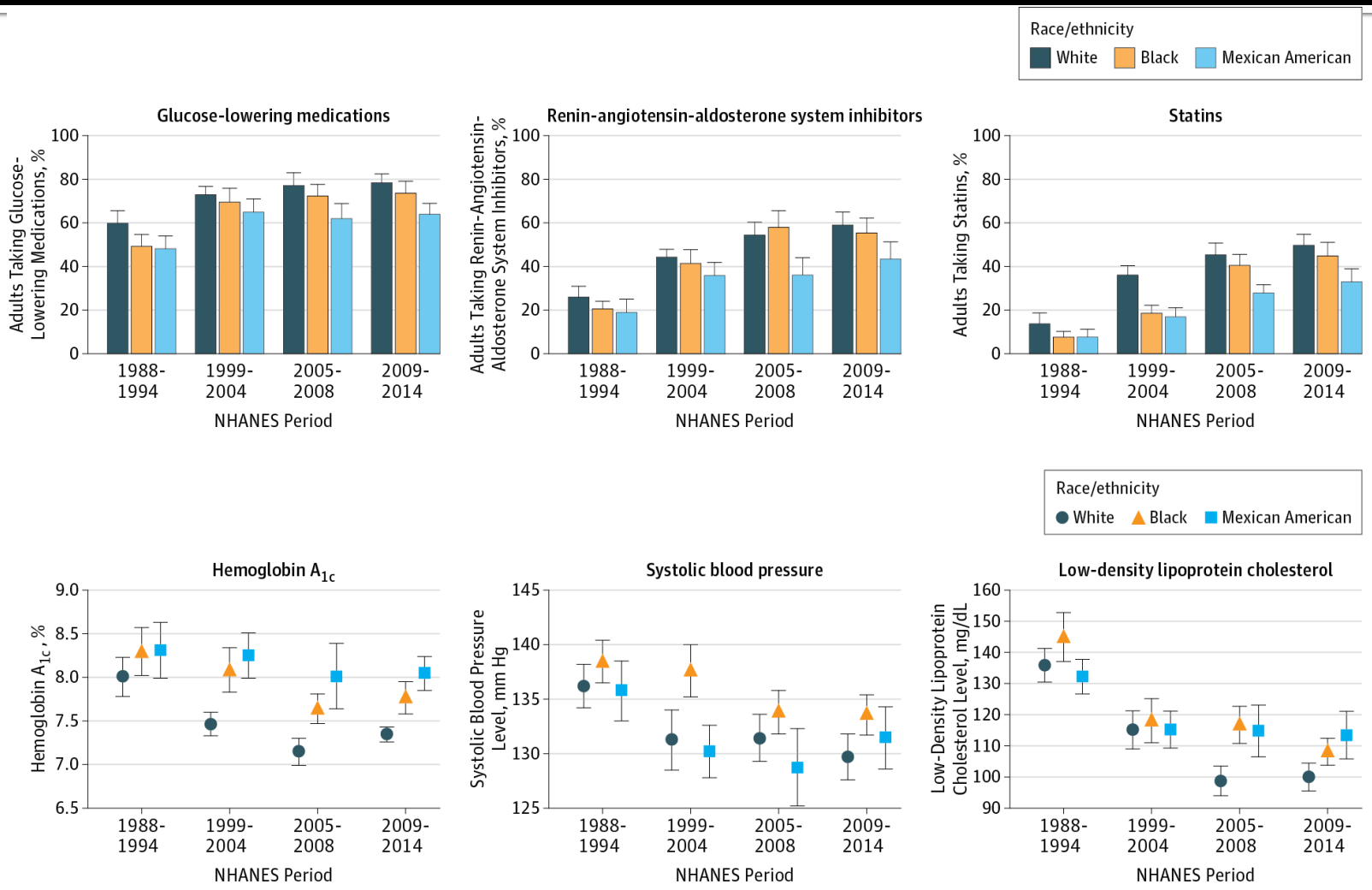


Hospital Readmission Rates



Annual Report, *USRDS 2016*

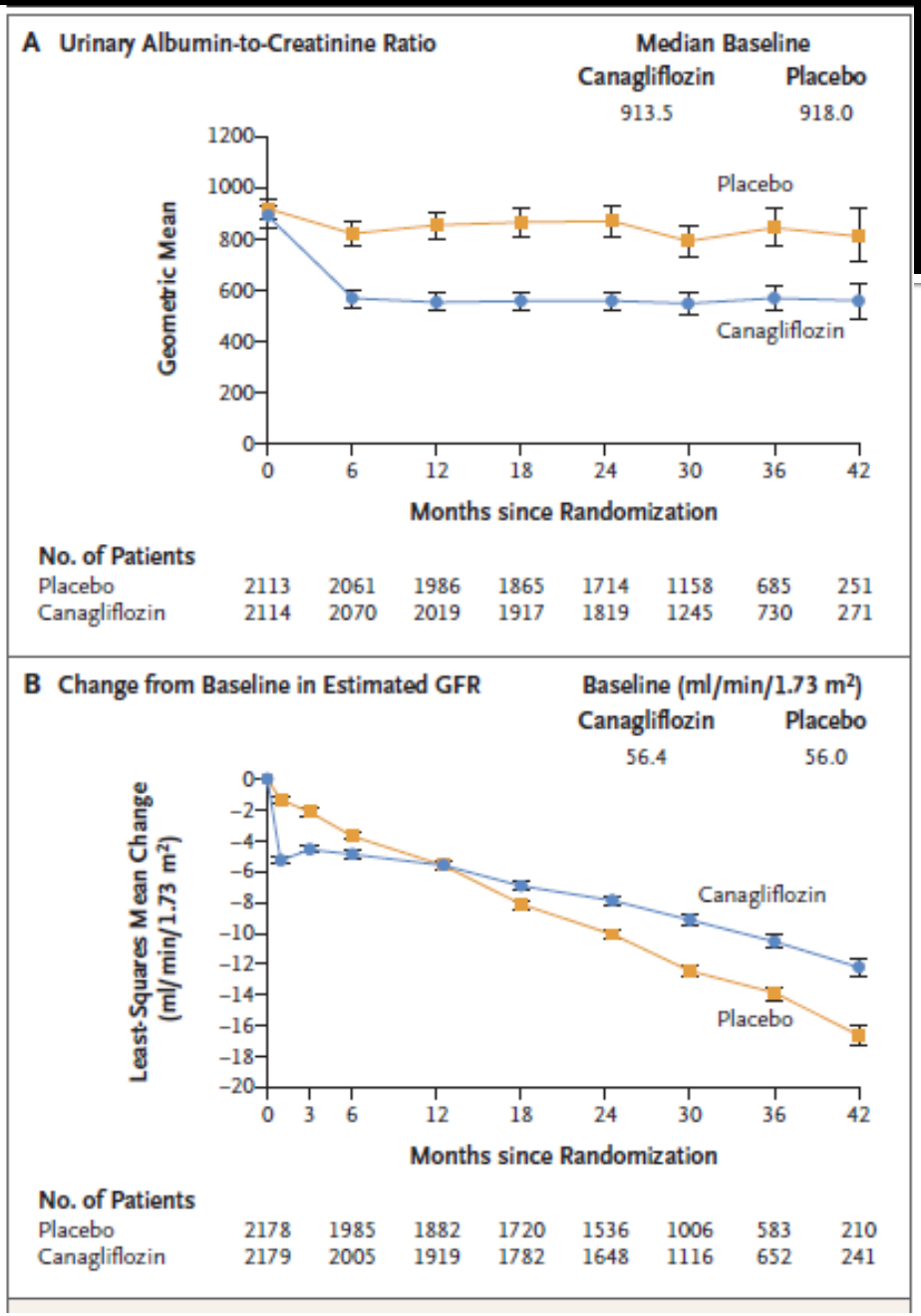
Change in diabetes care over time



Afkarian JAMA 2016

Credence

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



Perkovic et al, NEJM 2019

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 delay now than ever before:
  - Bicarbonate
  - SLGT2
  - ACE/ARB
  - BP Control
  - DM Control

References

- Perkovic et al, Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy, NEJM 2019
- Li et al, Longitudinal progression trajectory of GFR among patients with CKD, AJKD 2012
- Levey et al, A New Equation to Estimate Glomerular Filtration Rate, Ann Int Med 2009
- McMahon et al, Residual Lifetime Risk of CKD, NDT 2016
- Shlipak et al, Cystatin C versus Creatinine in Determining Risk Based on Kidney Function, NEJM 2013