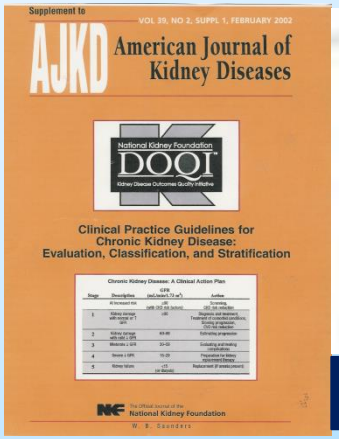
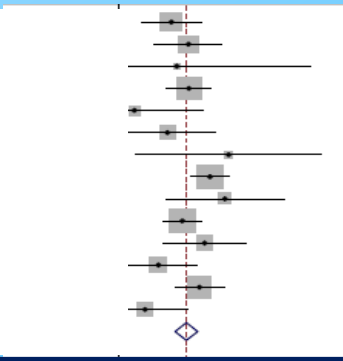
Chronic Kidney Disease (CKD) Measurement, Prevalence and Risk Factors

Epidemiology of A Modern Day Epidemic

Josef Coresh, MD, PhD

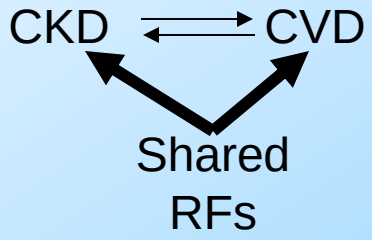
7/23/2014





Chronic Kidney Disease Prognosis Consortium (CKD-PC)

Outline



- CKD background
  - End-stage renal disease (ESRD) epidemic
  - Tip of the iceberg vs. the base
- Pathophysiology
- CKD in the population
  - Stages of CKD – kidney function
    - kidney damage – persistent proteinuria even with normal of mildly reduced kidney function
  - Estimating kidney function (GFR <- serum Cr + formula + calibration)
- Conditions associated with different stages of CKD (consequences)
  - [Diabetes], Hypertension, Anemia, Left ventricular geometry, Poor nutrition, bone disease
  - CVD [next lecture]
- Risk factors for ESRD & CKD progression

Global Kidney Disease 1

Evolving importance of kidney disease: from subspecialty to global health burden

Kai-Uwe Eckardt, Josef Coresh, Olivier Devuyst, Richard J Johnson, Anna Köttgen, Andrew S Levey, Adeera Levin

The Lancet; 382:158 - 169, 13 July 2013

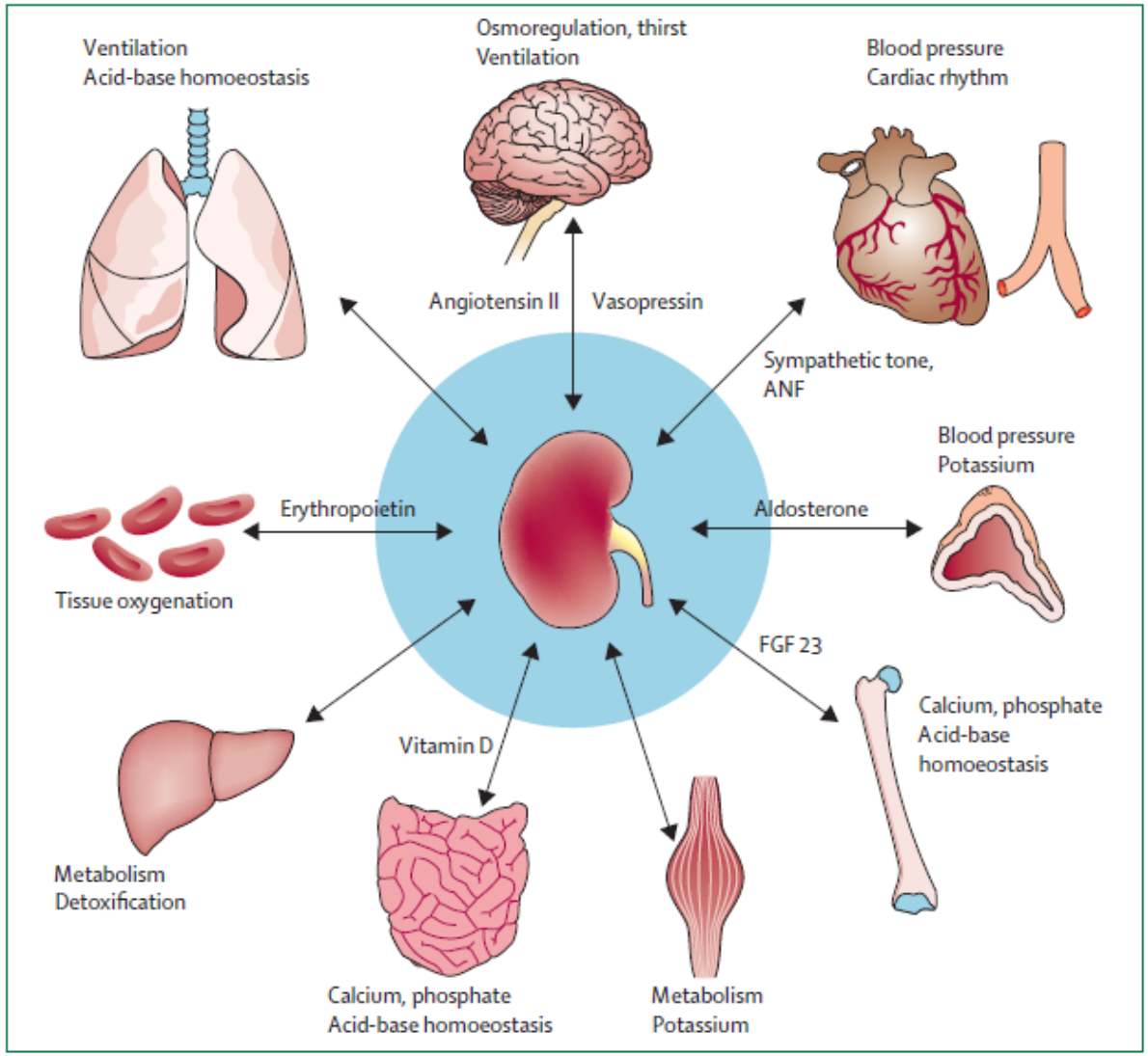


Figure 2: **Effect of kidney function on essential homoeostatic processes**

Definition and Classification of CKD: **Clinical** vs. **Epidemiologic** Context

	KDOQI (2002) KDIGO (2004)	Epidemiologic Studies
Definition		
"Damage" Structure	Pathology Markers (urine, blood, imaging) Transplant	Urine alb/creat (**ACR**) >30 mg/g
Function	GFR <60 ml/min/1.73 m^2 (less than ½ the normal value in young adults)	**eGFR** <60 ml/min/1.73 m^2
Duration	>3 months	**Single** measurement
Classification (Stage)		
Function	GFR >90, 60-89, 30-59, 15-29, <15	eGFR >90, 60-89, 30-59, 15-29, <15

CKD Standardized Definitions: 2000-2002 K/DOQI CKD Definition

OPINION ARTICLE

Chronic Renal Confusion: Insufficiency, Failure, Dysfunction, or Disease

Chi-yuan Hsu, MD, and Glenn M. Chertow, MD

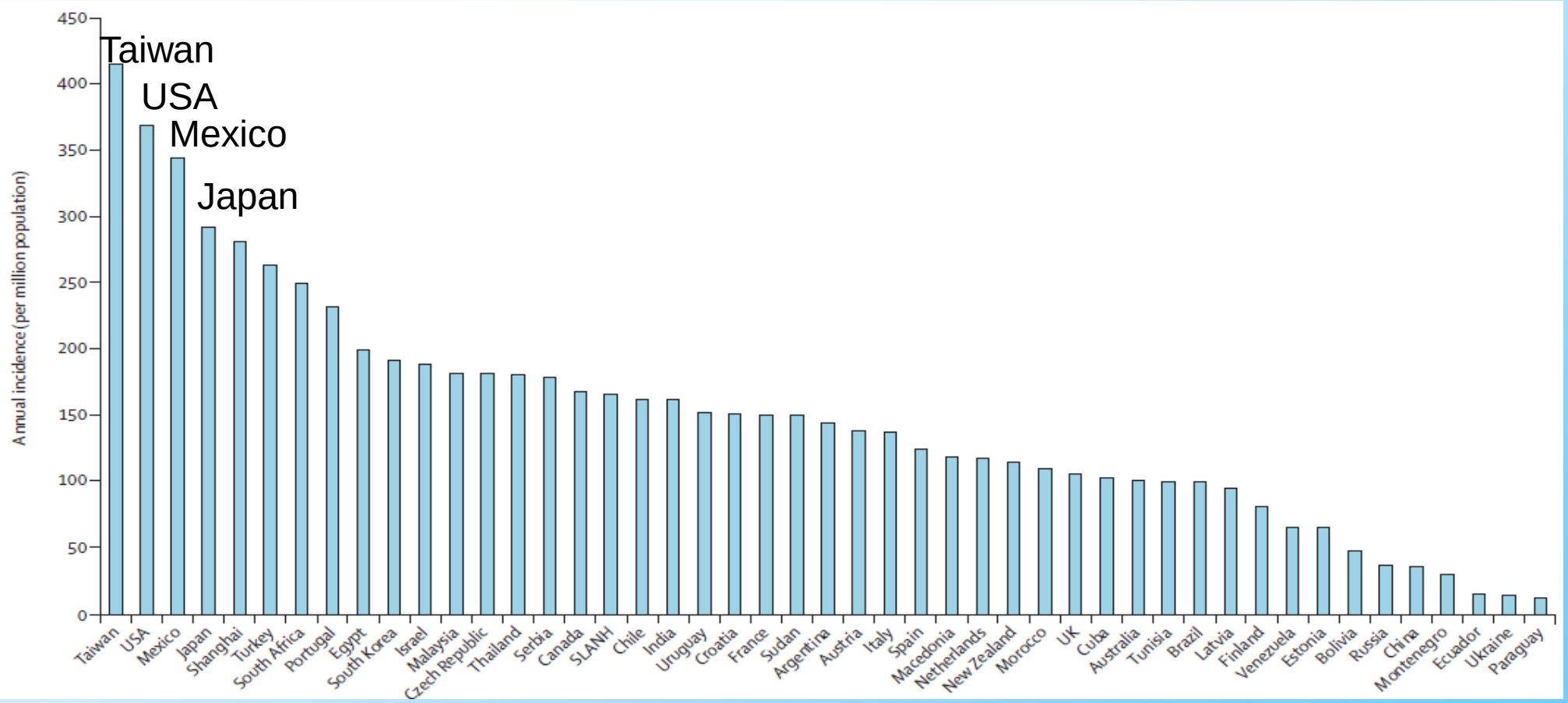
Table 3. Objective Findings Corresponding to Semiquantitative Descriptors: ASN Abstracts

Abstract No.		Descriptor	Range of Renal Function
1998	712*	"Mild"	Serum creatinine 1.5-3.0 mg/dL
	746*	"Mild"	Serum creatinine 1.54-3.0 mg/dL in men, 1.36-3.0 mg/dL in women
	760	"Moderate or advanced"	Several categories of serum creatinine, all >1.4 mg/dL
	767*	"Severe"	Creatinine clearance <25 mL/min with and without hemodialysis
	771	"Moderate"	Creatinine clearance 20-60 mL/min
	774*	"Severe"	GFR 2-10 mL/min or on dialysis
	828*	"Severe"	"Renal clearance" <30 mL/min
1999	783	"Mild"	Serum creatinine 1.0-1.4, 1.5-2.5 mg/dL, or MDRD estimated GFR 50-70, and <50 mL/min
	801*	"Mild"	Serum creatinine >96 μmol/L (>1.1 mg/dL)
	828	"Moderate"	Serum creatinine 300-500 μmol/L (3.4-5.6 mg/dL)
	829	"Advanced"	Serum creatinine ≥500 μmol/L (5.6 mg/dL)
	860*	"Moderate"	Creatinine clearance <60 mL/min
	903*	"Mild"	Serum creatinine 1.5-3.0 mg/dL

* Term used in abstract title

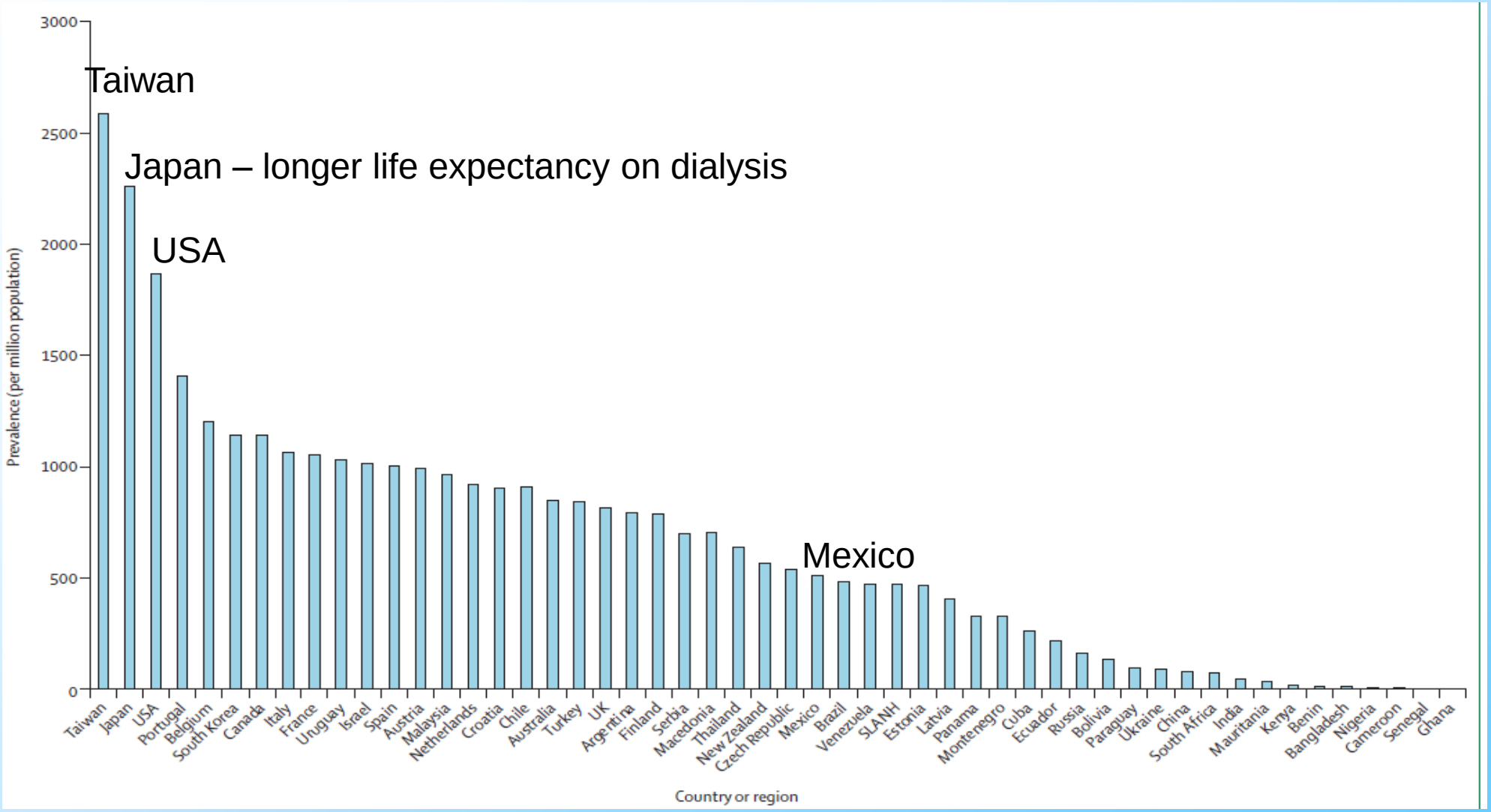
Am J of Kidney Dis, 2000; 36:415-418

ESRD Incidence Internationally



***Lancet* 2013; 382: 260–72**

ESRD Prevalence



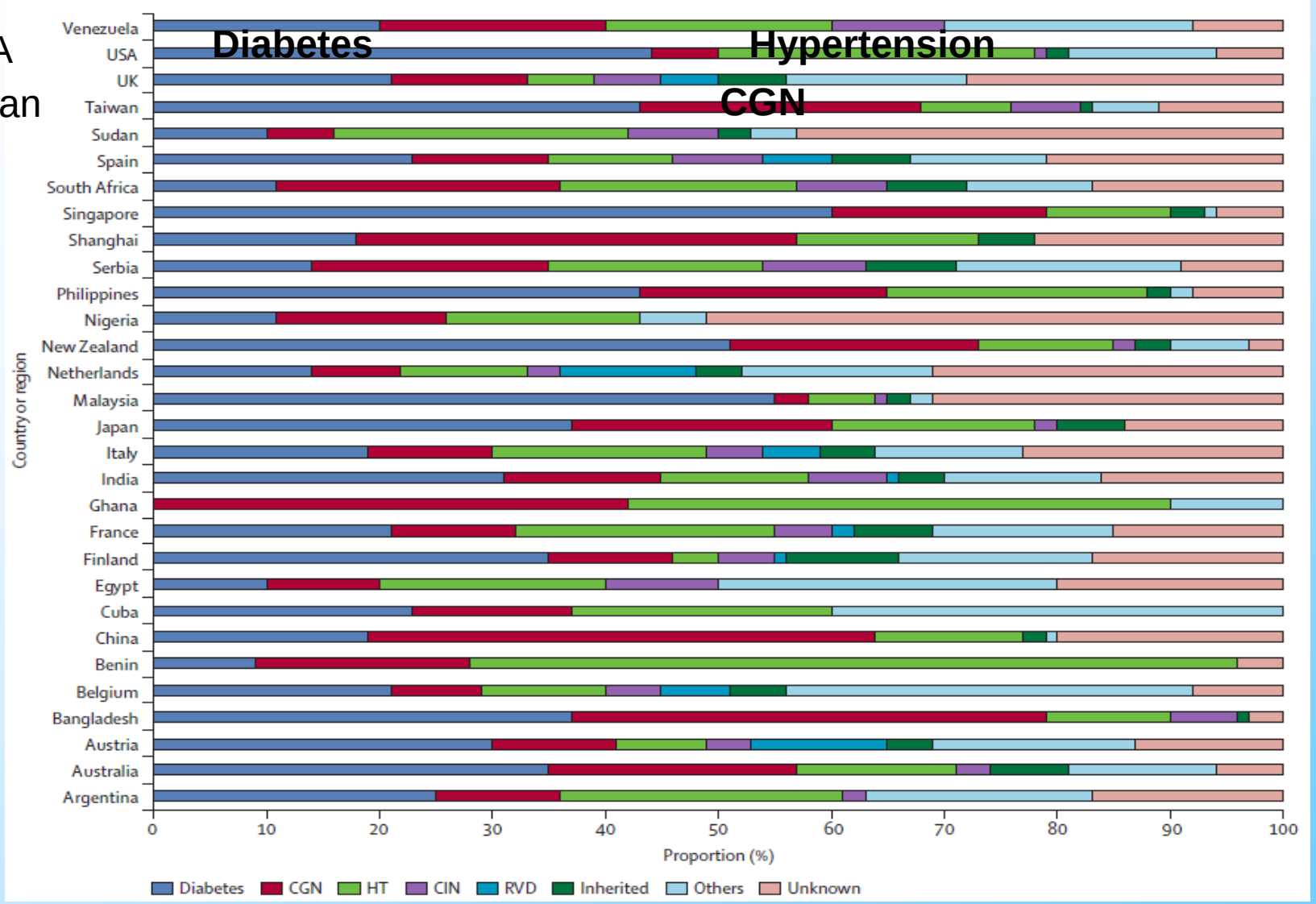
***Lancet* 2013; 382: 260–72**

Reported Causes of ESRD

USA

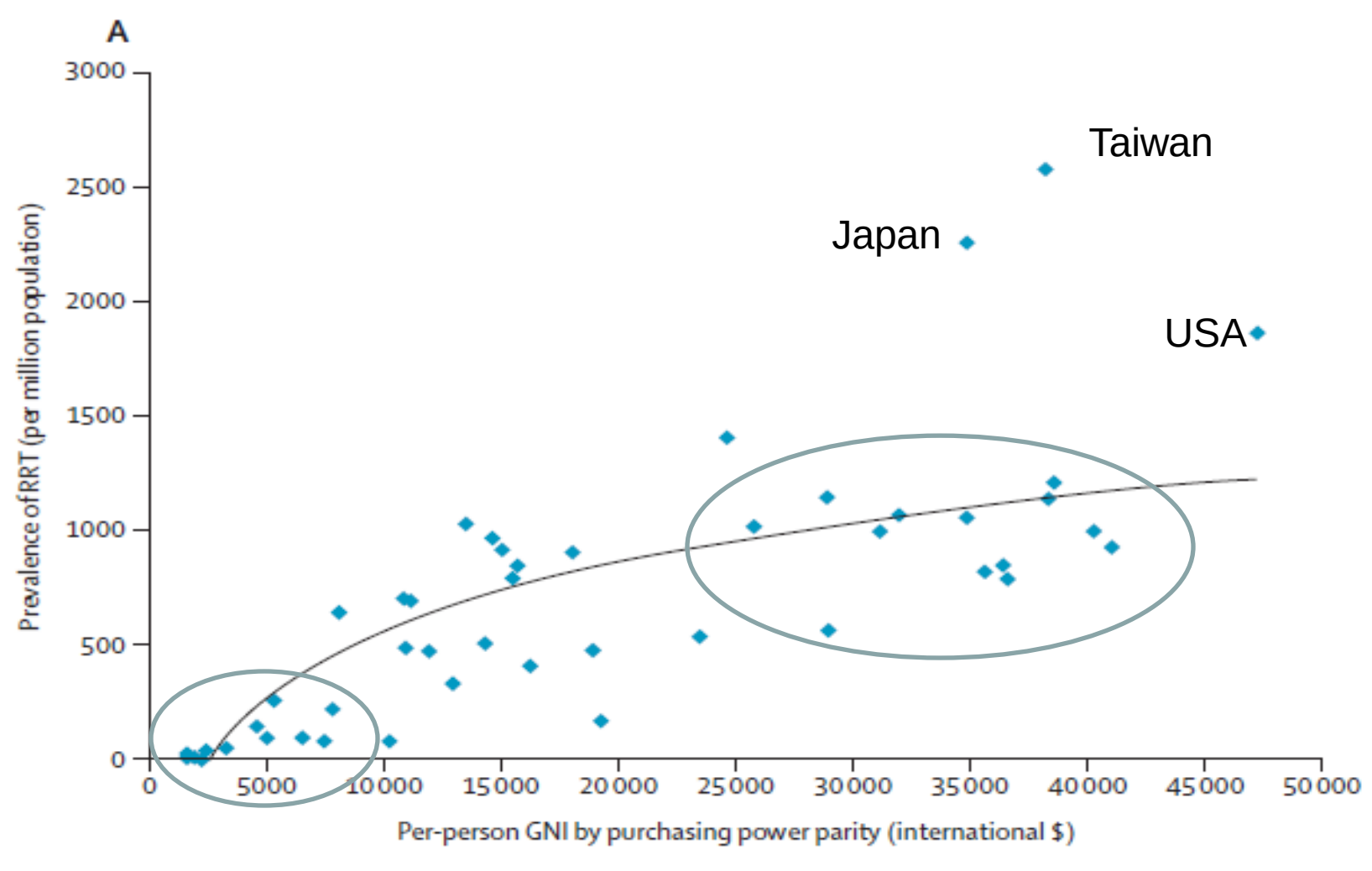
Taiwan

Japan



***Lancet* 2013; 382: 260–72**

Relationship of Prevalence of ESRD to Gross National Income (GNI) Per Person

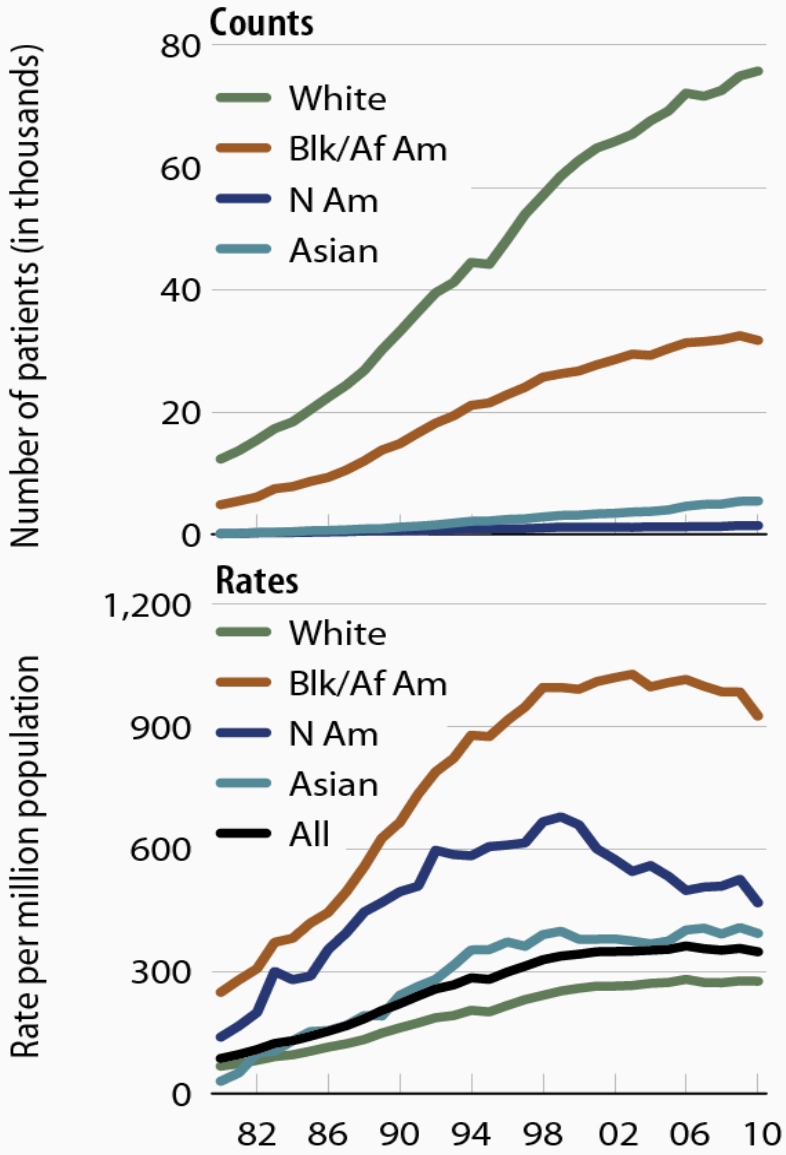


***Lancet* 2013; 382: 260–72**

Incident counts & adjusted rates of ESRD, by race

Figure 1.5 (Volume 2)

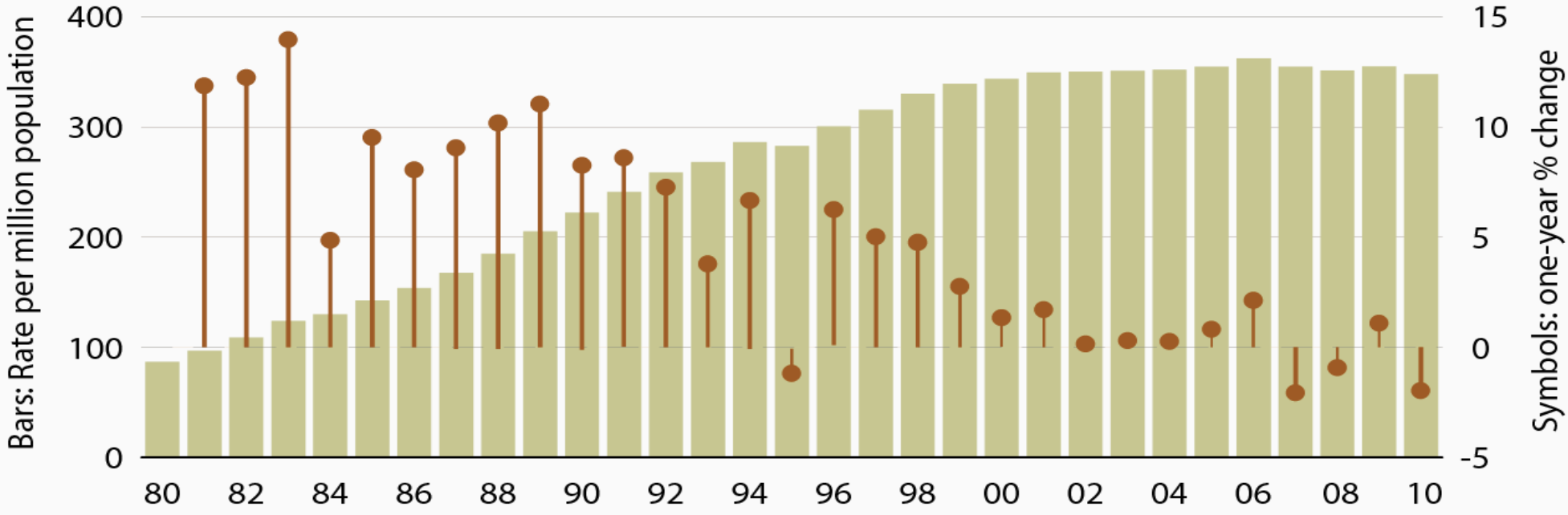
- ESRD Prevalence in 2010: 594,374 patients (415,000 Dialysis, 179,000 transplant)
  - 61% White
  - 32% African-American
  - 1.4% Native American
  - 5.5% Asian, Pacific-Islander
- Gender: 57% male
- Physician designed "Cause"
  - **37.8% Diabetes**
  - **24.8% Hypertension**
  - 14.6% Glomerulonephritis
  - 4.8% Cystic disease
- Total costs: $47.5 B ($29 B medicare)



USRDS 2012 ADR

Adjusted incident rates of ESRD & annual percent change

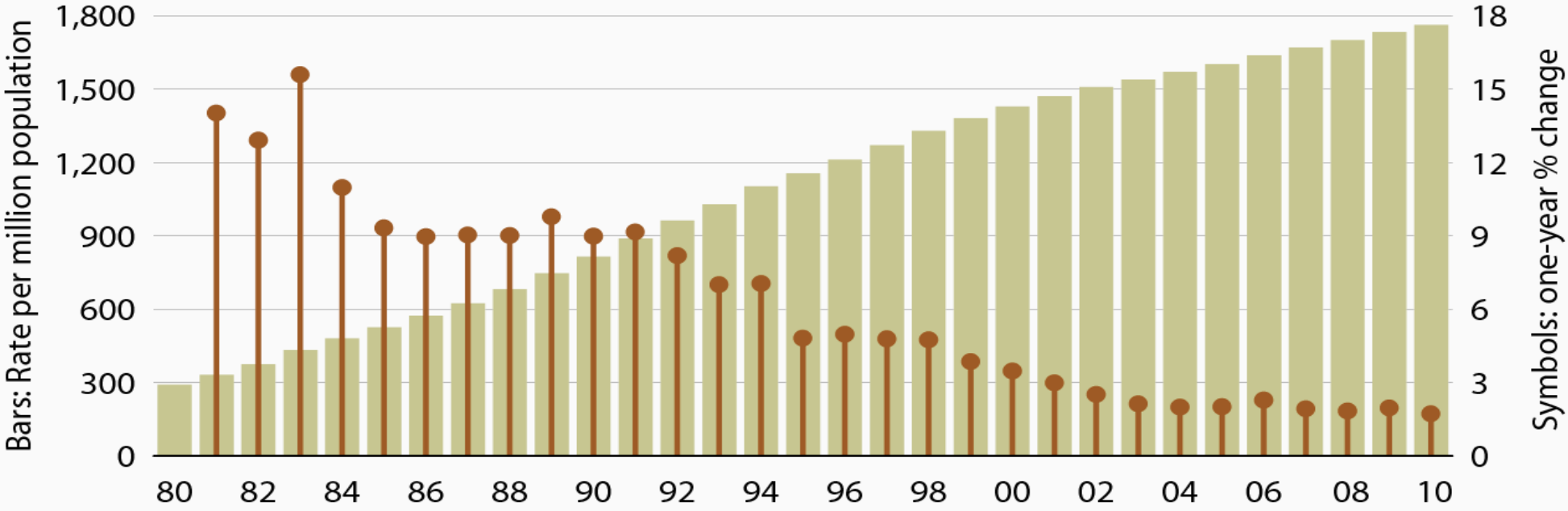
Figure 1.2 (Volume 2)



Incident ESRD patients. **Adj: age/gender/race**; ref: 2005 ESRD patients.

Adjusted prevalent rates of ESRD & annual percent change

Figure 1.10 (Volume 2)



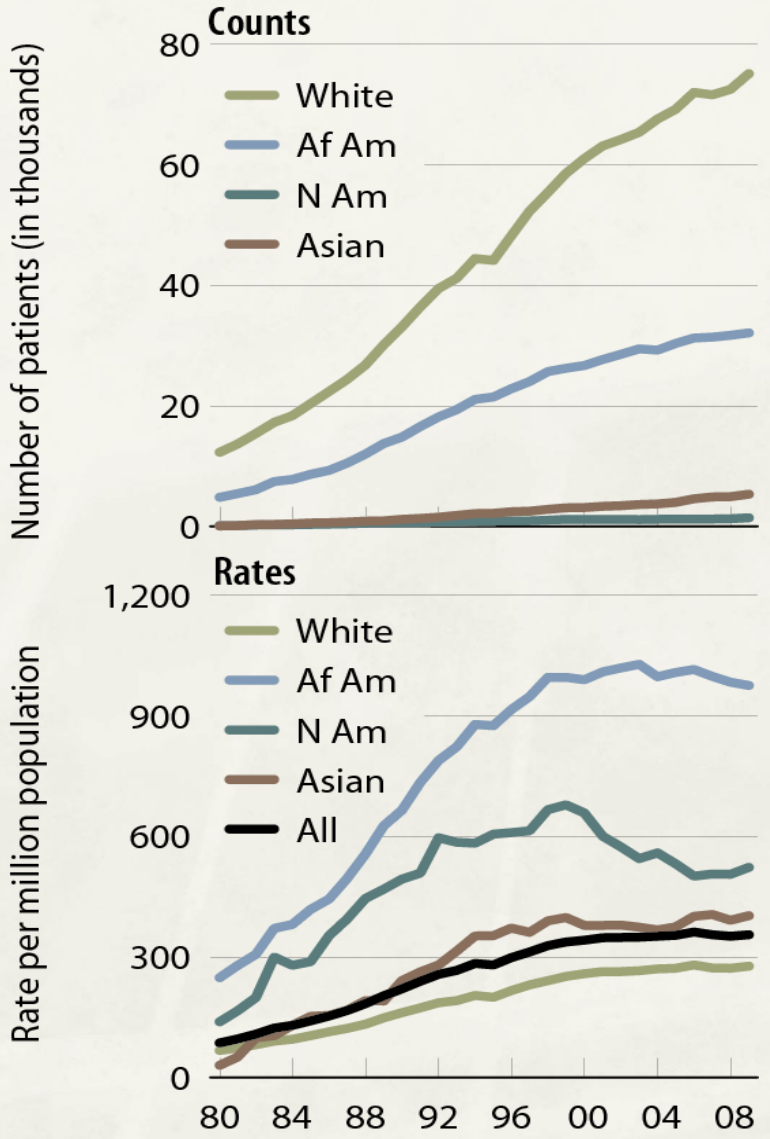
December 31 point prevalent ESRD patients.
Adj: age/gender/race; ref: 2005 ESRD patients.

USRDS 2012 ADR

Incident counts & adjusted rates of ESRD, by race

Figure 1.6 (Volume 2)

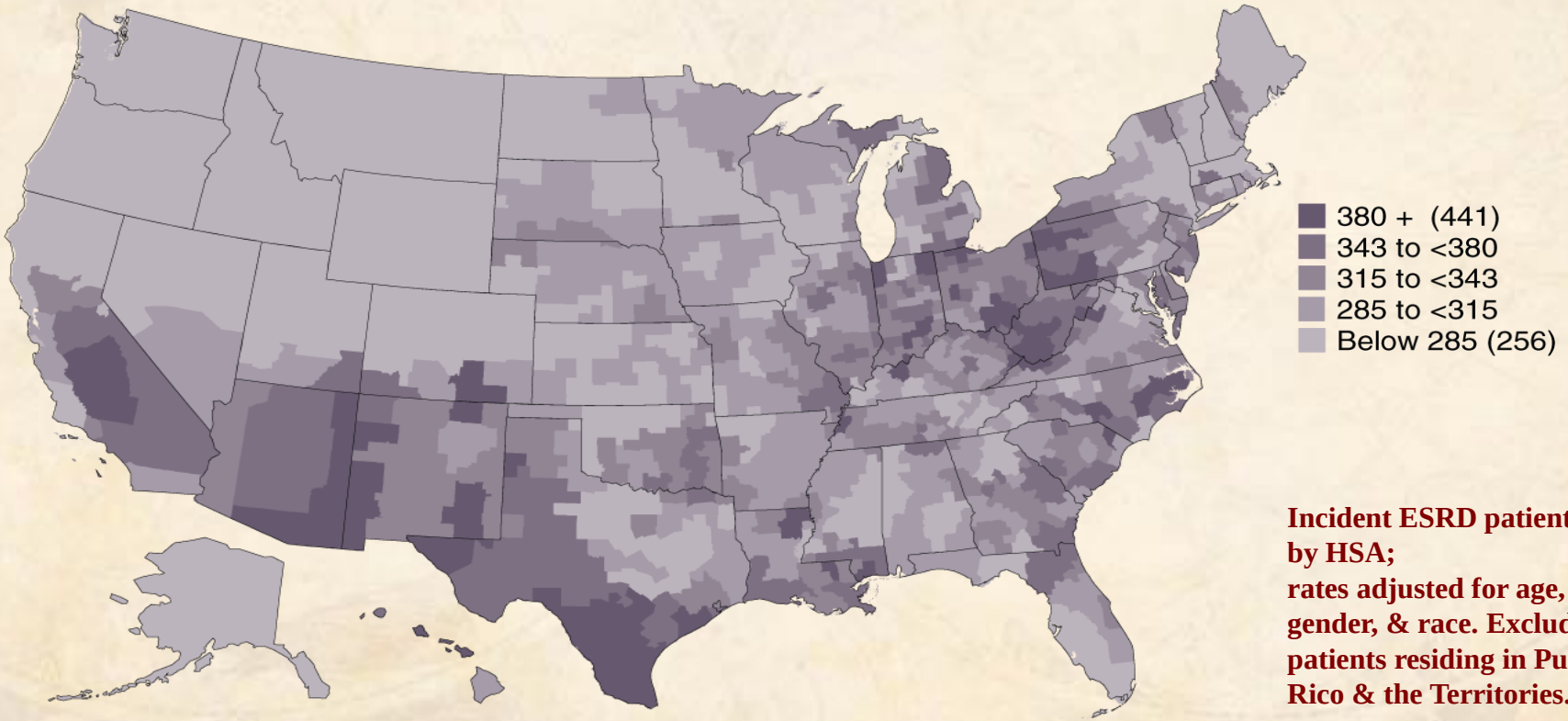
- Incidence counts still increasing
- Adjusted incidence rates have plateaued in all groups



Incident ESRD patients.
Adj: age/gender; ref: 2005 ESRD patients.

Geographic variations in adjusted incident rates (per million population), by HSA, 1998

Figure p.7 (Volume 2)

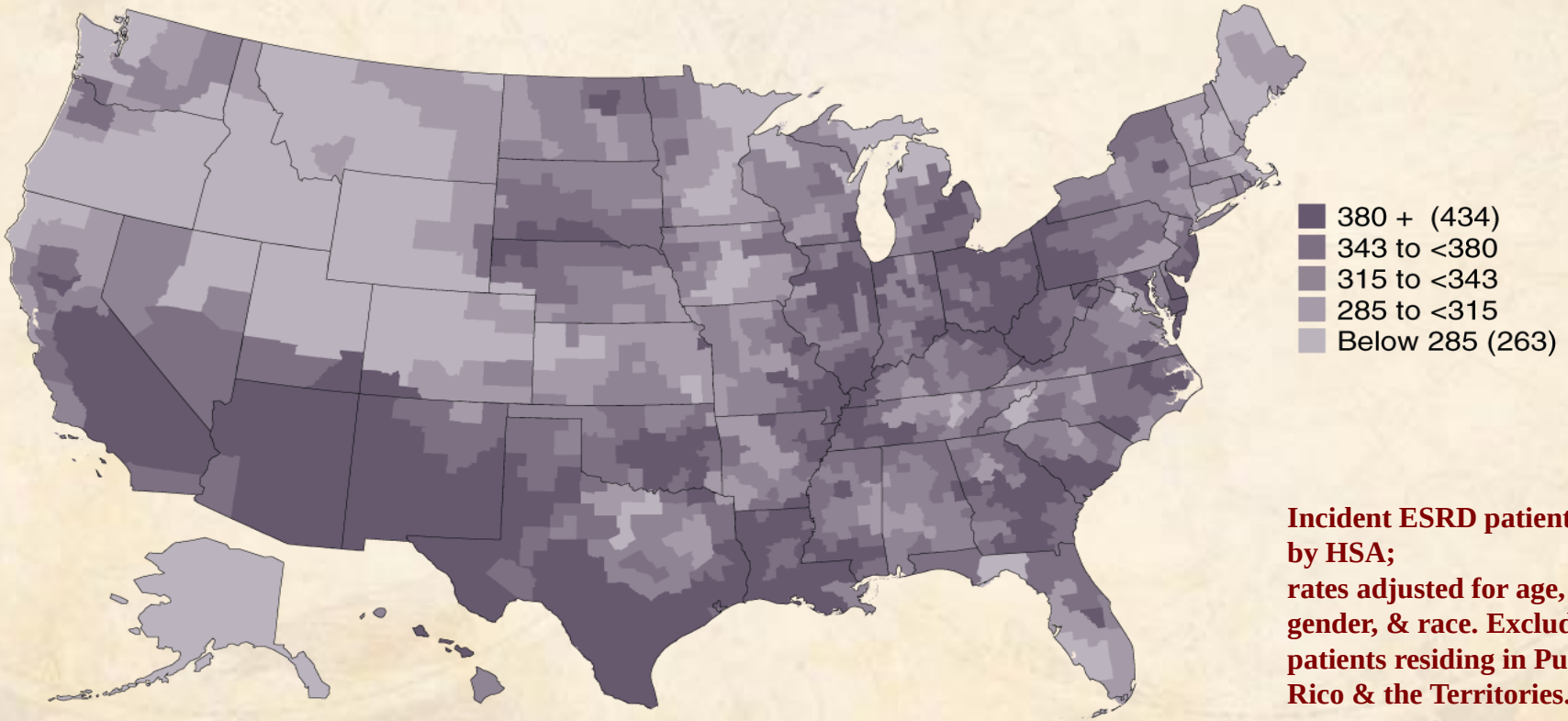


Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

USRDS

Geographic variations in adjusted incident rates (per million population), by HSA, 2003

Figure p.7 (continued; Volume 2)

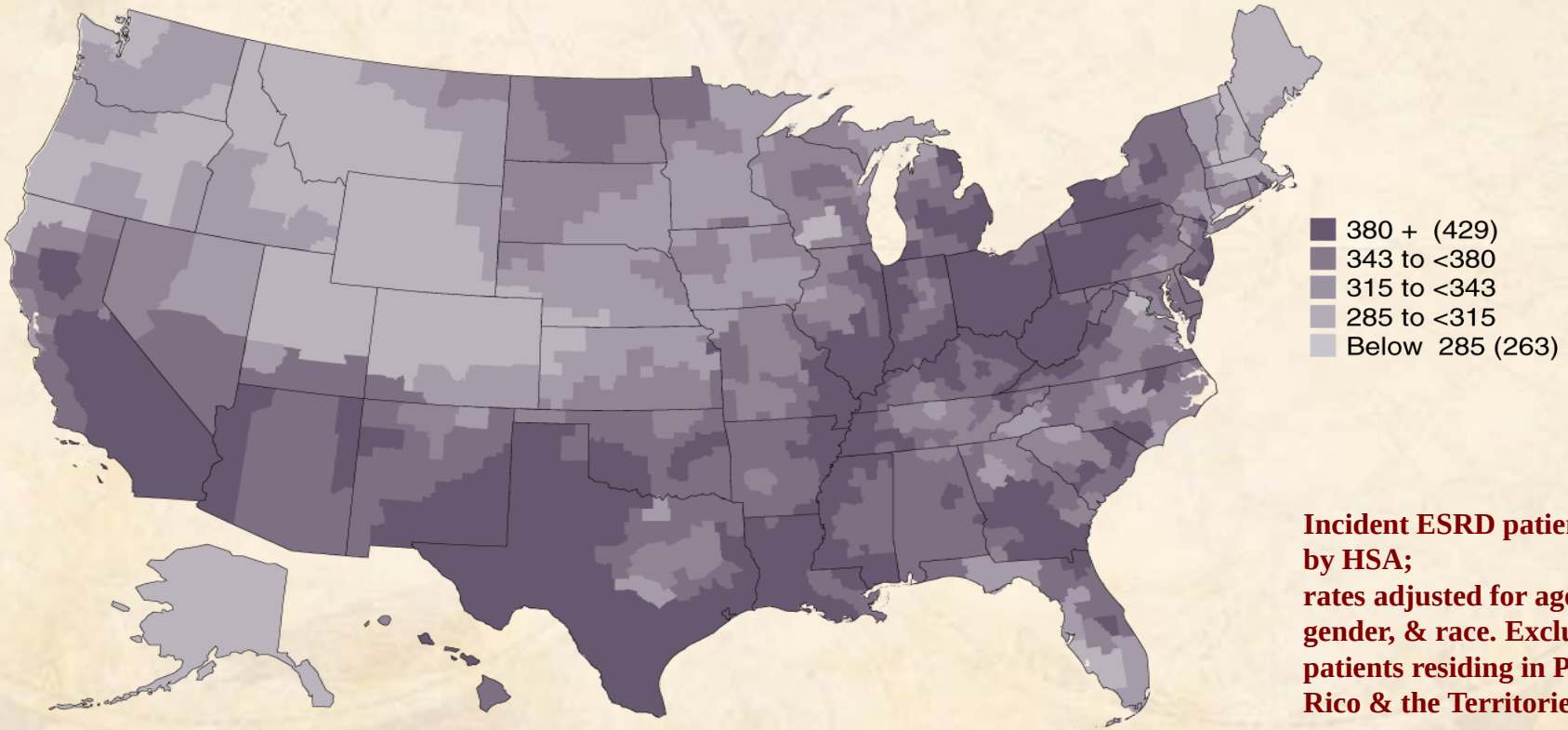


Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

USRDS

Geographic variations in adjusted incident rates (per million population), by HSA, 2008

Figure p.7 (continued; Volume 2)



Incident ESRD patients, by HSA; rates adjusted for age, gender, & race. Excludes patients residing in Puerto Rico & the Territories.

USRDS

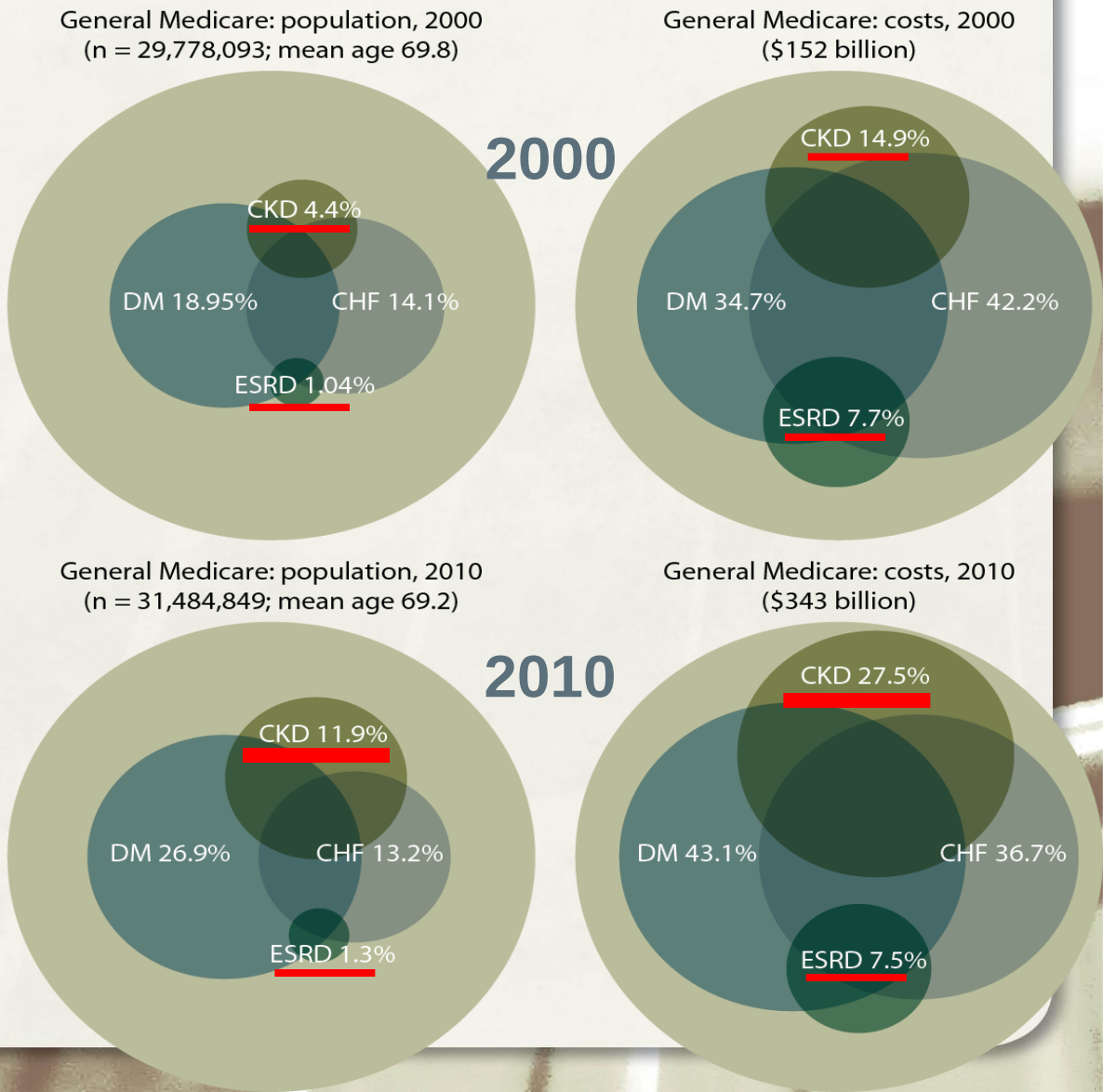
Distribution Medicare Patients & Costs for CKD, CHF, diabetes, & ESRD, 2000 & 2010

- High cost growing population

HOWEVER –

- Under-diagnosis of CKD has decreased over time explaining some of the marked increase in "**diagnosed**" CKD

- Distinguish – costs "with" vs. costs "for" CKD/ESRD

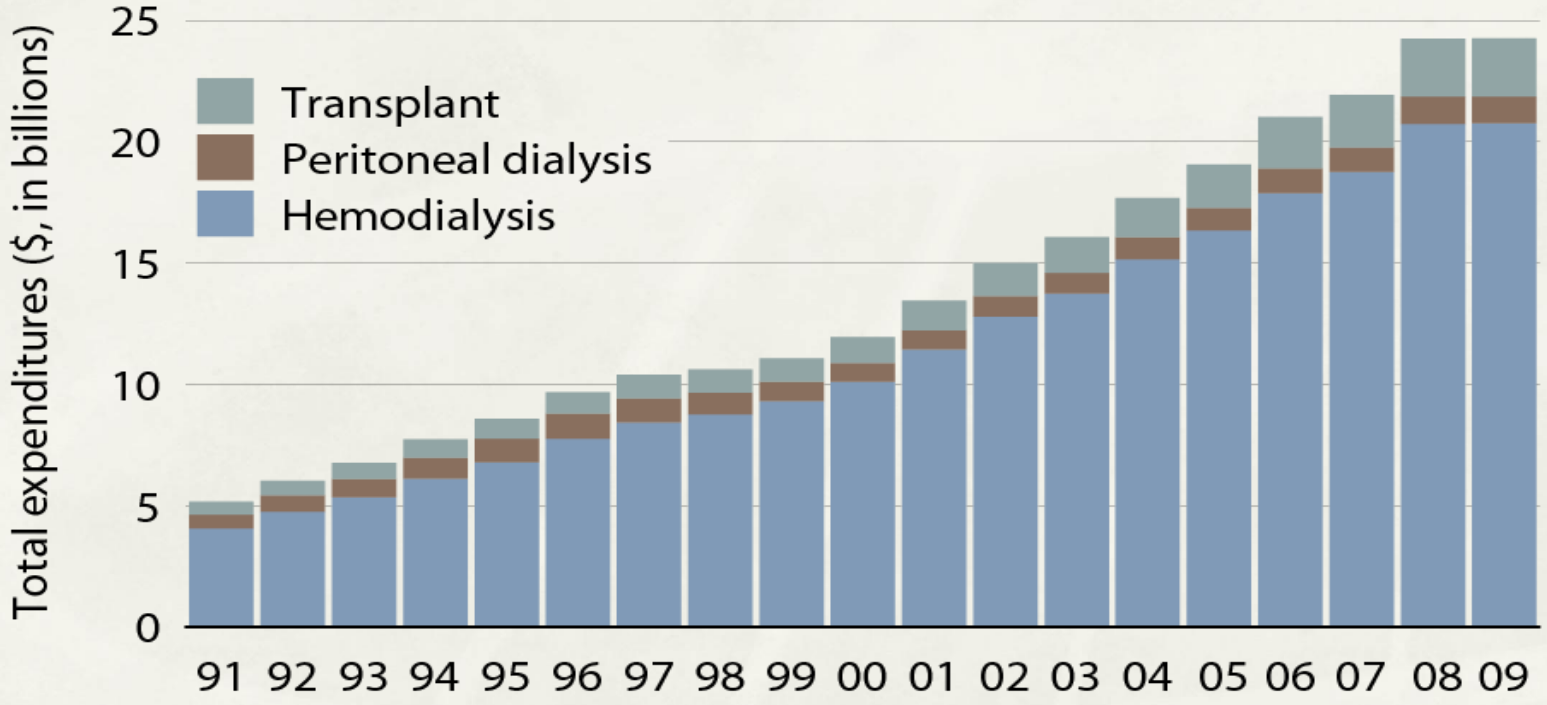


USRDS 2011ADR

USRDS 2012 ADR

Total Medicare ESRD expenditures, by modality

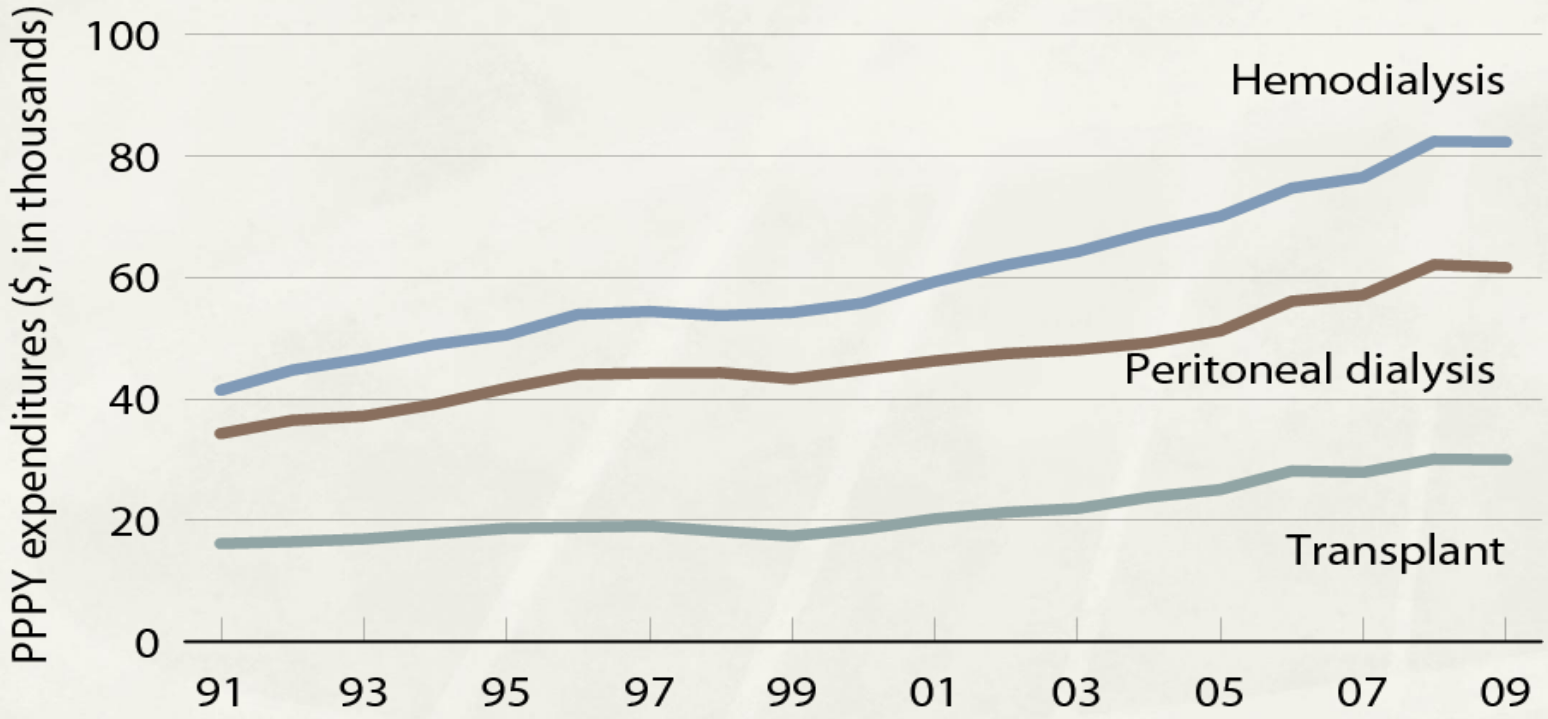
Figure 11.6 (Volume 2)



Period prevalent ESRD patients, patients with Medicare as secondary payor are excluded.

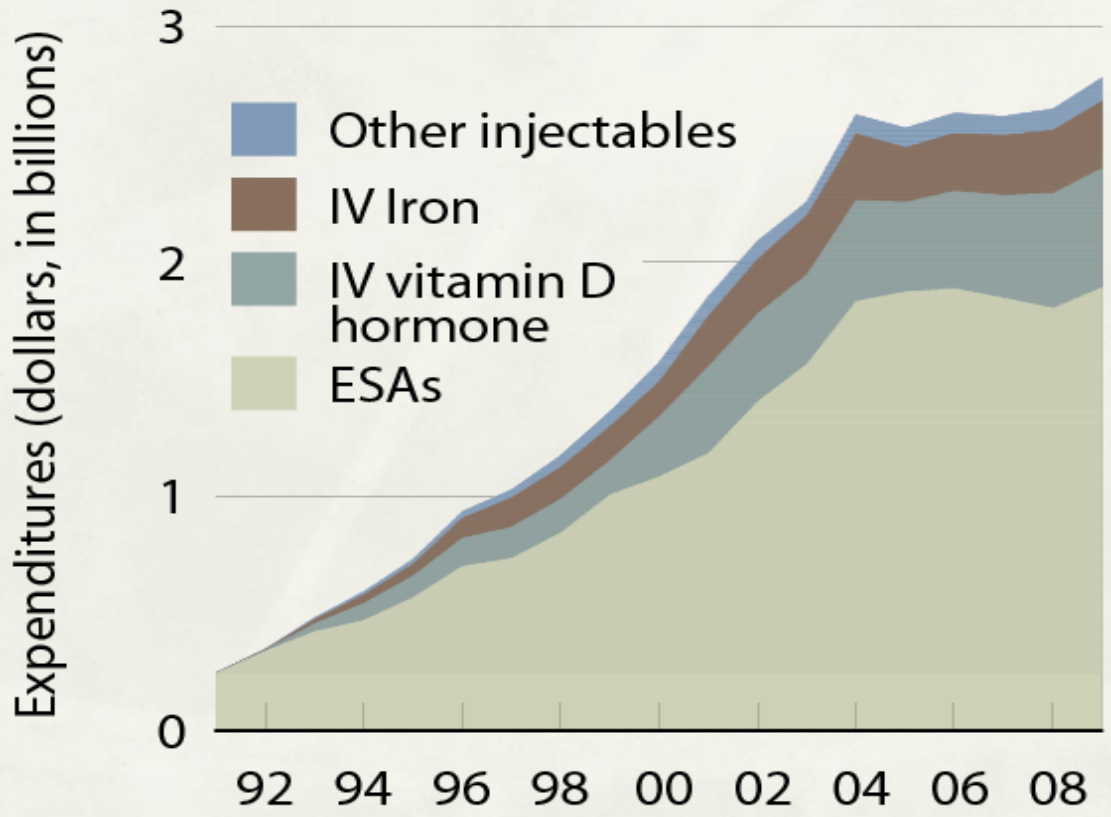
Total Medicare ESRD expenditures per person per year, by modality

Figure 11.7 (Volume 2)



Total Medicare spending for injectables

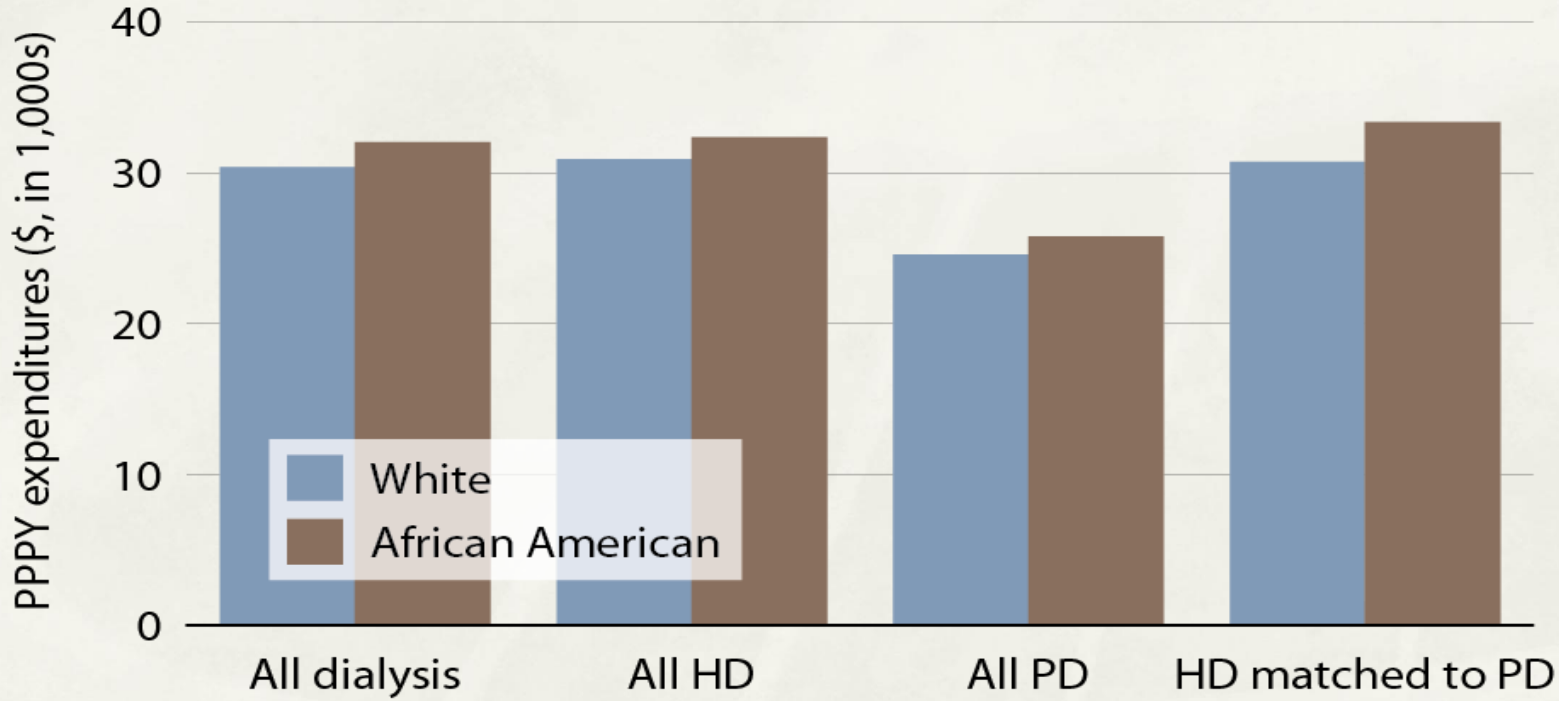
Figure 11.9 (Volume 2)



Period prevalent dialysis patients.

Total PPPY outpatient expenditures, by dialysis modality & race, 2009

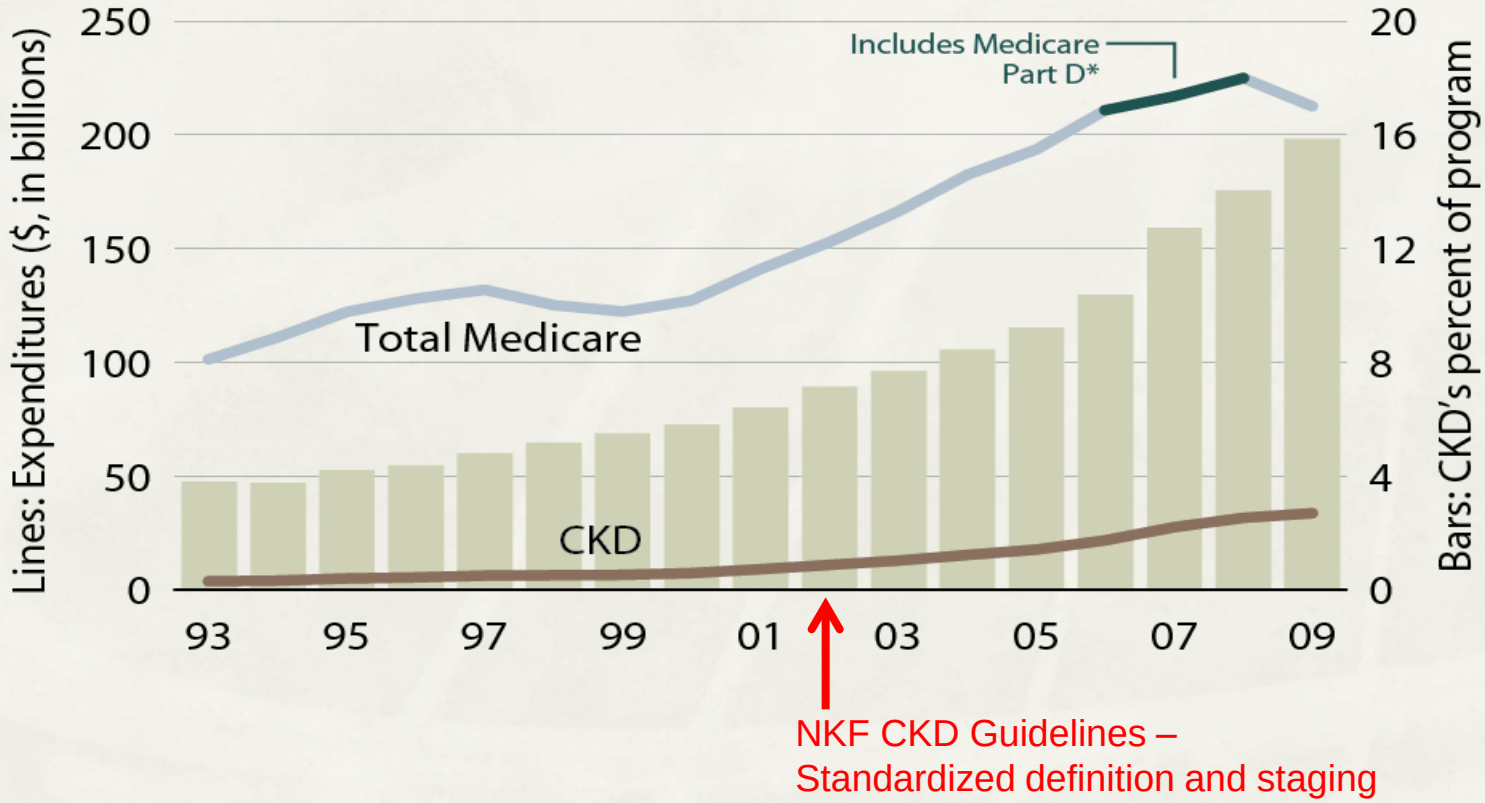
Figure 11.19 (Volume 2)



Period prevalent dialysis patients, 2009.

Overall expenditures for CKD in the Medicare population

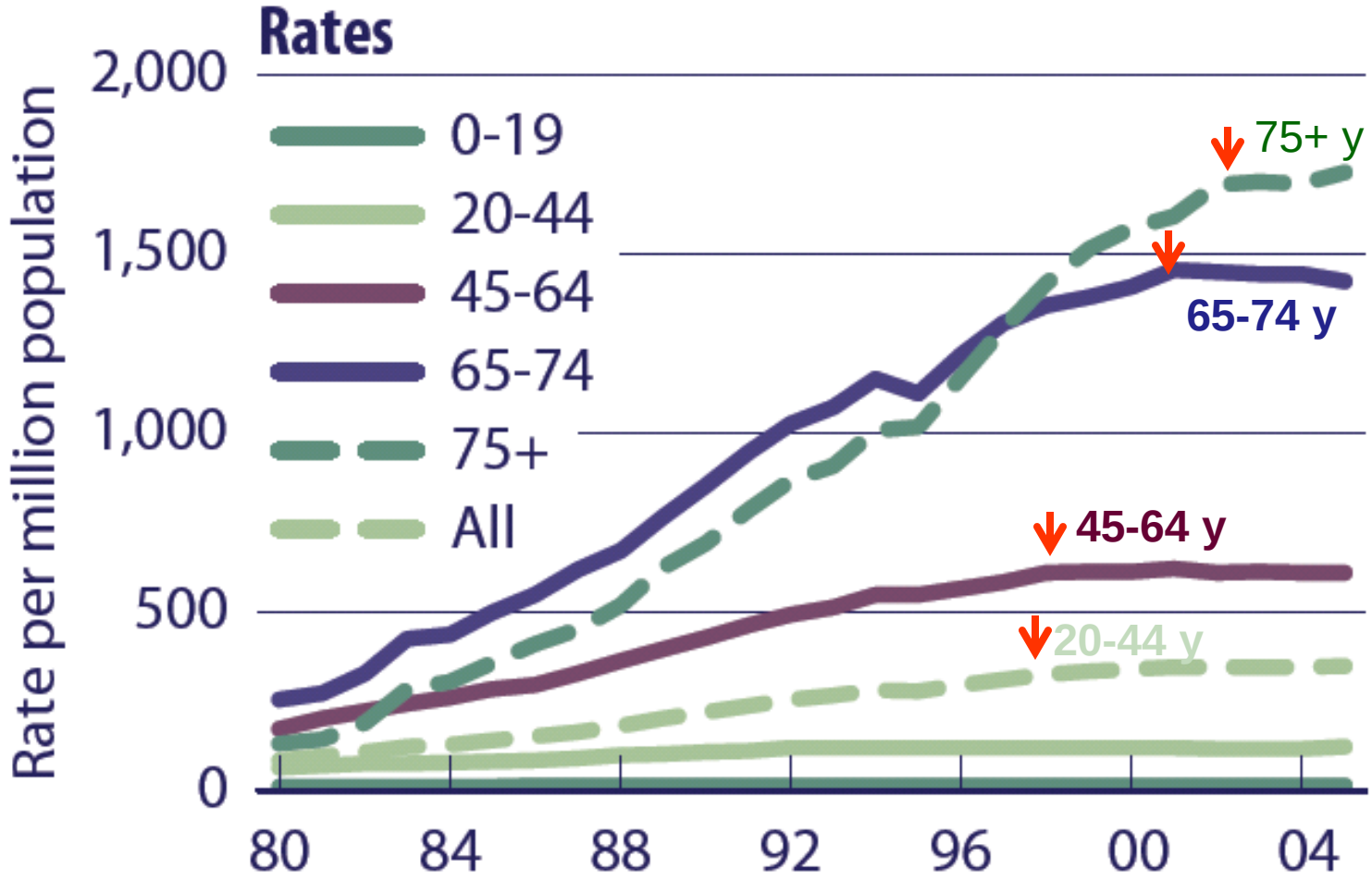
Figure 6.5 (Volume 1)



Point prevalent Medicare patients age 65 & older. *Medicare Part D data not available for 2009.

USRDS

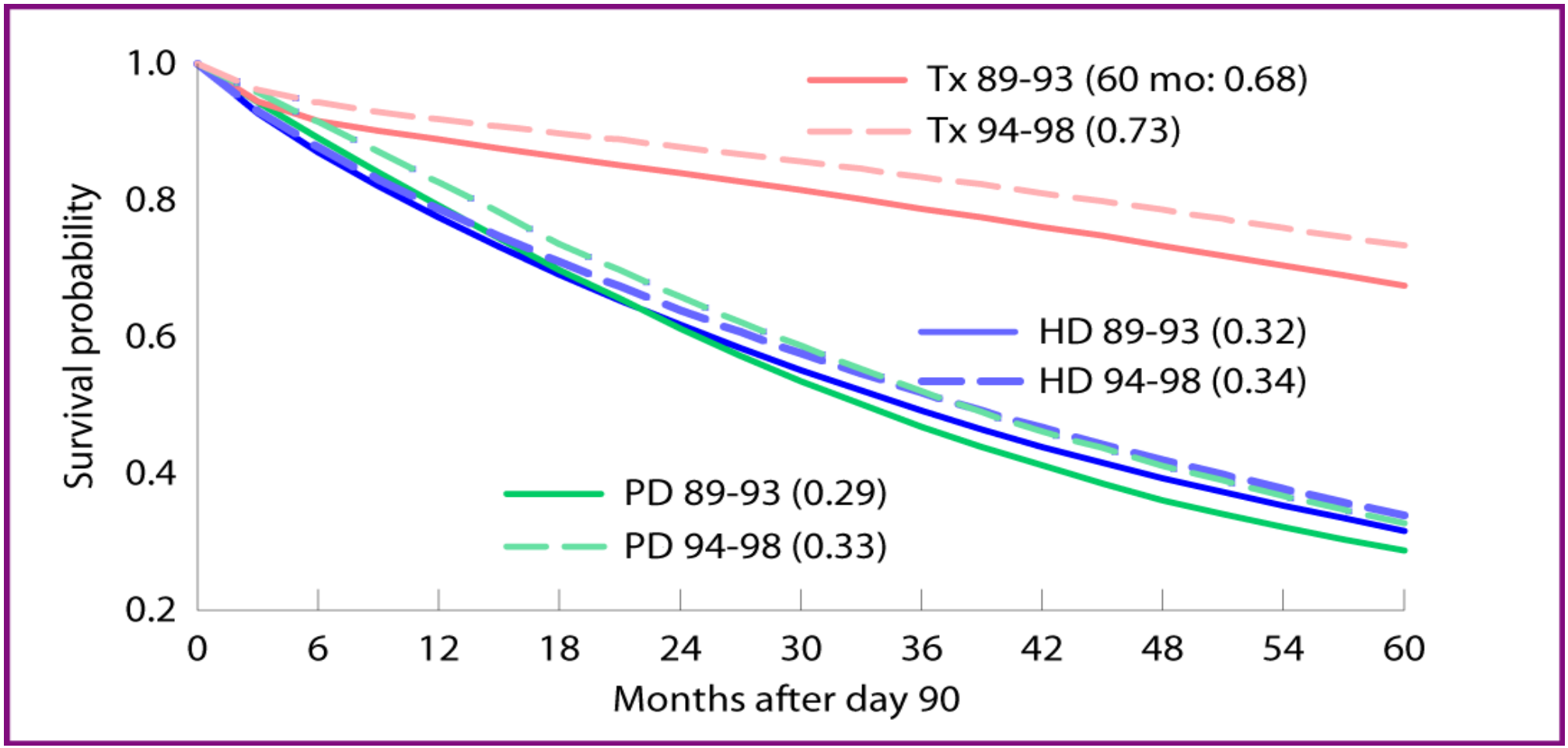
Increasing Rates Plateau Later at Older Ages (suggests improved access/acceptance of treatment)



USRDS

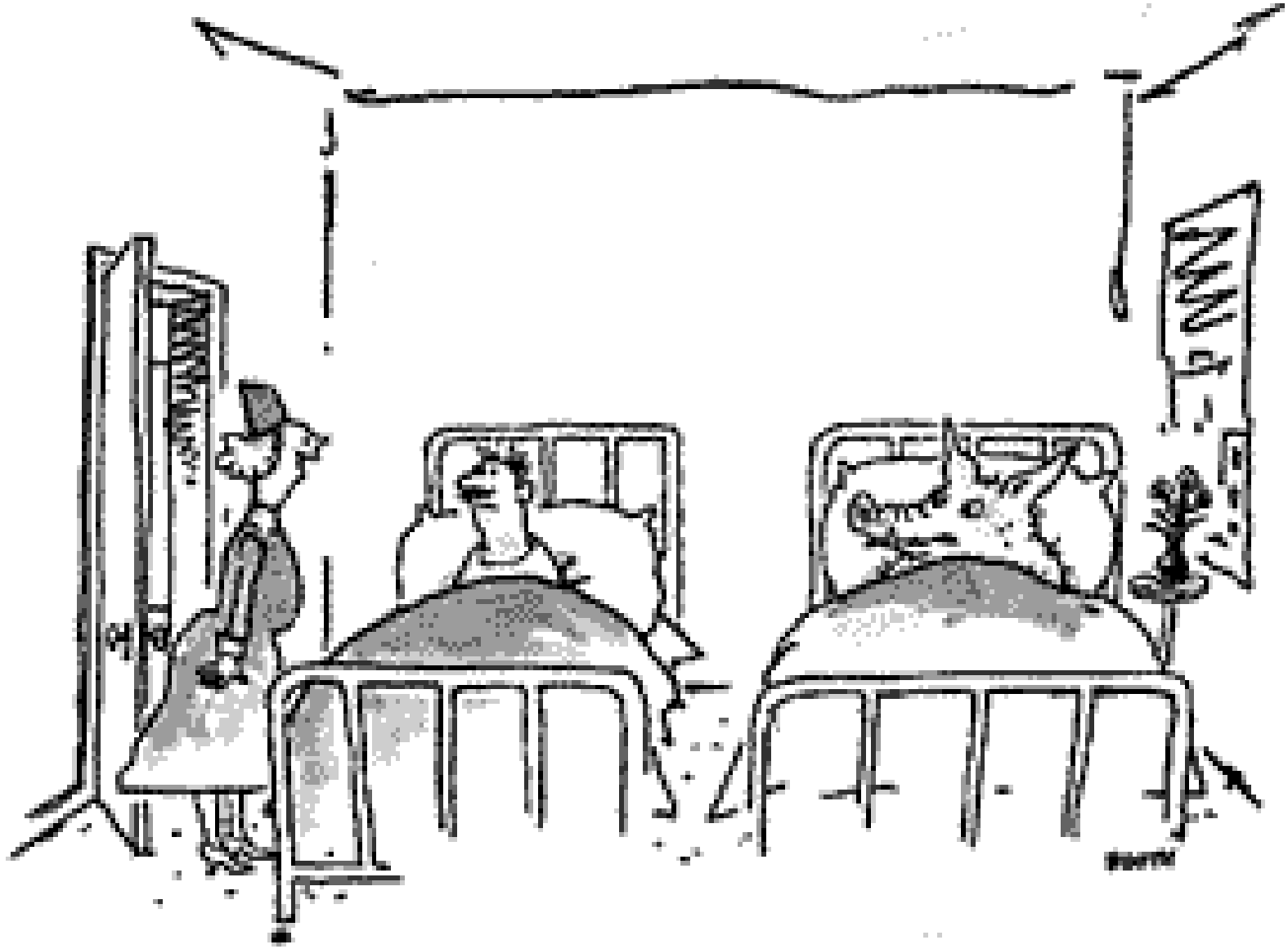
Adjusted five-year survival, by first modality

Figure p.25

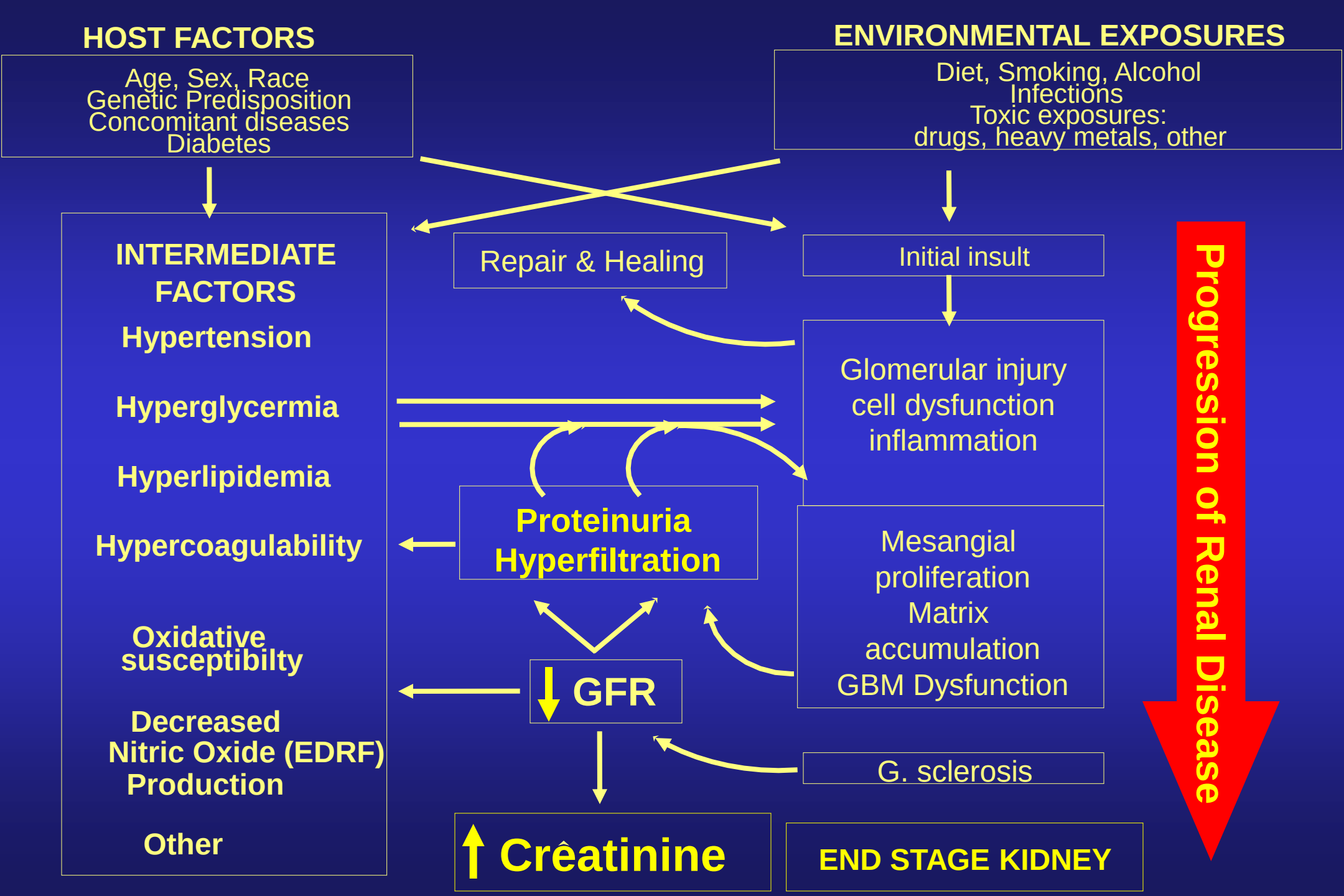


Incident patients; adjusted for age, gender, race, & primary diagnosis. 1996, used as reference cohort.

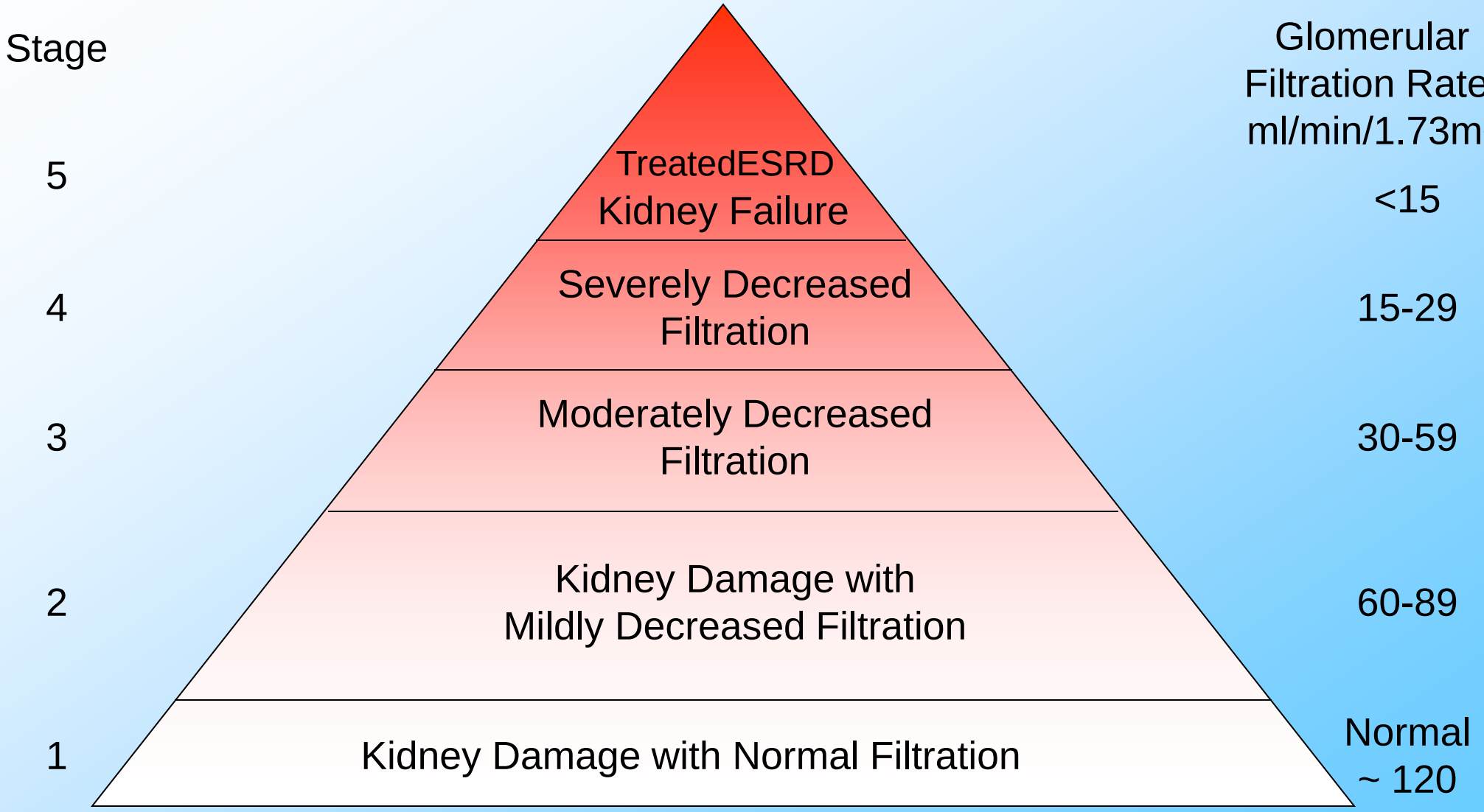
USRDS

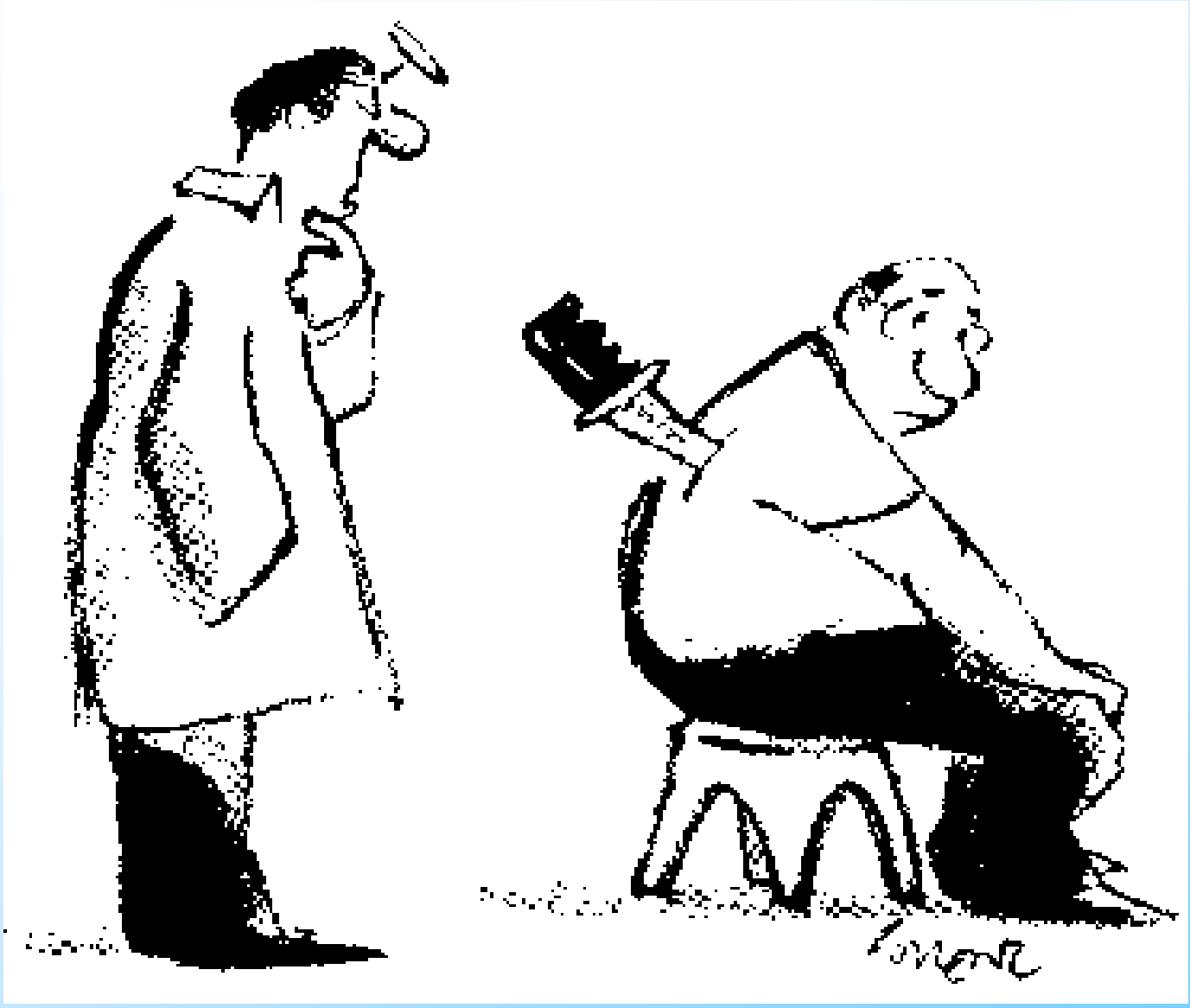


"Good news, Mr. Herndon. We worked out the budget, and we have a kidney."


HOST FACTORS
Age, Sex, Race
Genetic Predisposition
Concomitant diseases
Diabetes
ENVIRONMENTAL EXPOSURES
Diet, Smoking, Alcohol
Infections
Toxic exposures:
drugs, heavy metals, other
INTERMEDIATE FACTORS
Hypertension
Hyperglycermia
Hyperlipidemia
Hypercoagulability
Oxidative susceptibilty
Decreased Nitric Oxide (EDRF) Production
Other
Repair & Healing
Initial insult
Glomerular injury
cell dysfunction
inflammation
Proteinuria
Hyperfiltration
Mesangial proliferation
Matrix accumulation
GBM Dysfunction
GFR
G. sclerosis
Crêatinine
END STAGE KIDNEY
Progression of Renal Disease

Stages of Chronic Kidney Disease



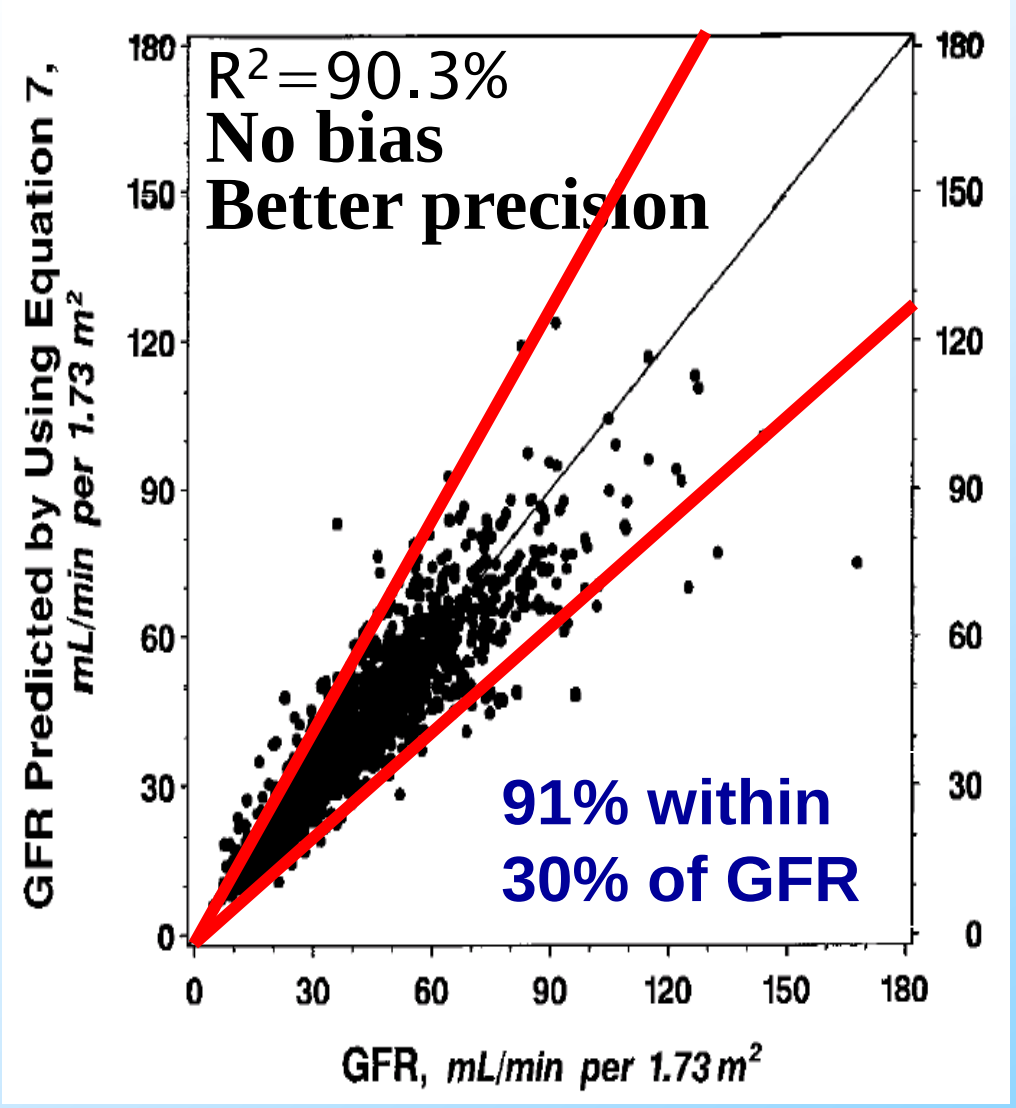


“It’s got to come out, of course, but that doesn’t address the deeper problem.”

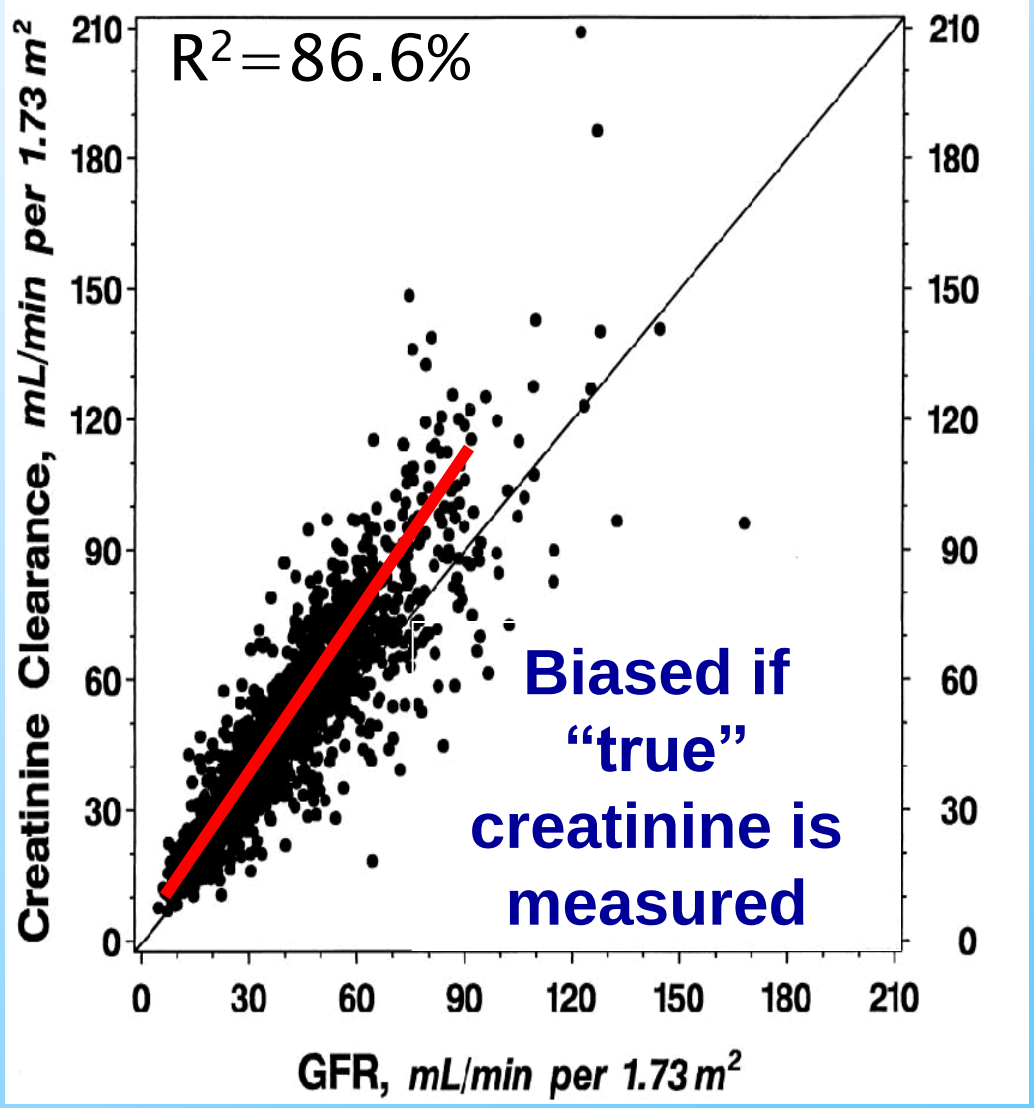
Prevalence of CKD - Methodology

- Estimating GFR
  - **Equations using serum creatinine** vs. Iothalamate GFR
  - Using serum creatinine alone wastes lots of information
- Calibration of serum creatinine
  - Precision (Good), Bias (currently Terrible)
- Standardization is important; <60 for defining CKD is conservative (compared to <80-90 which is ~2 SD below normal for young adults) allowing for some imprecision in calibration
- Precision of GFR estimates based on equations
  - Better at lower GFR
- Estimating progression of CKD
  - Slope vs. time to event
  - Rise in serum creatinine vs.change in GFR estimate

MDRD study equation

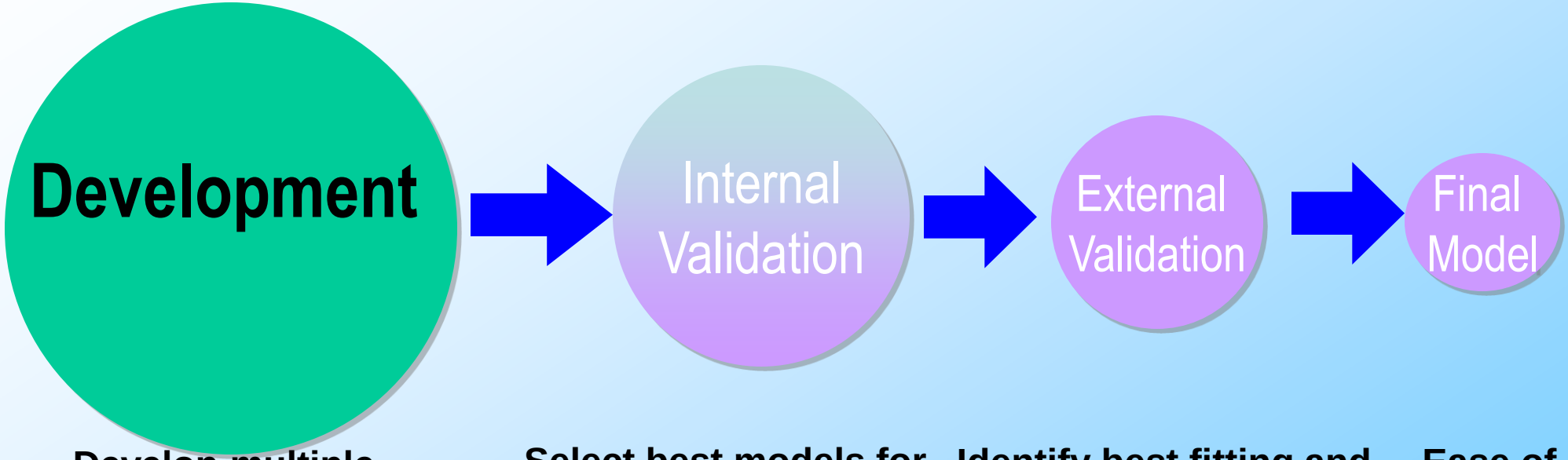


24-hour creatinine clearance



Levey et al *Ann Intern Med* 1999

Phases in Model Development and Selection



Develop multiple models; Compare complex to simpler models using 2/3 of data

Select best models for external validation; Validate and compare within base models using 1/3 of data

Identify best fitting and most generalizable models; Comparison among base models

Ease of use in clinical practice

Category 1 (10 studies) Development 5,504 Internal validation 2,571	Category 2 (20 studies) 4,870	1 & 2

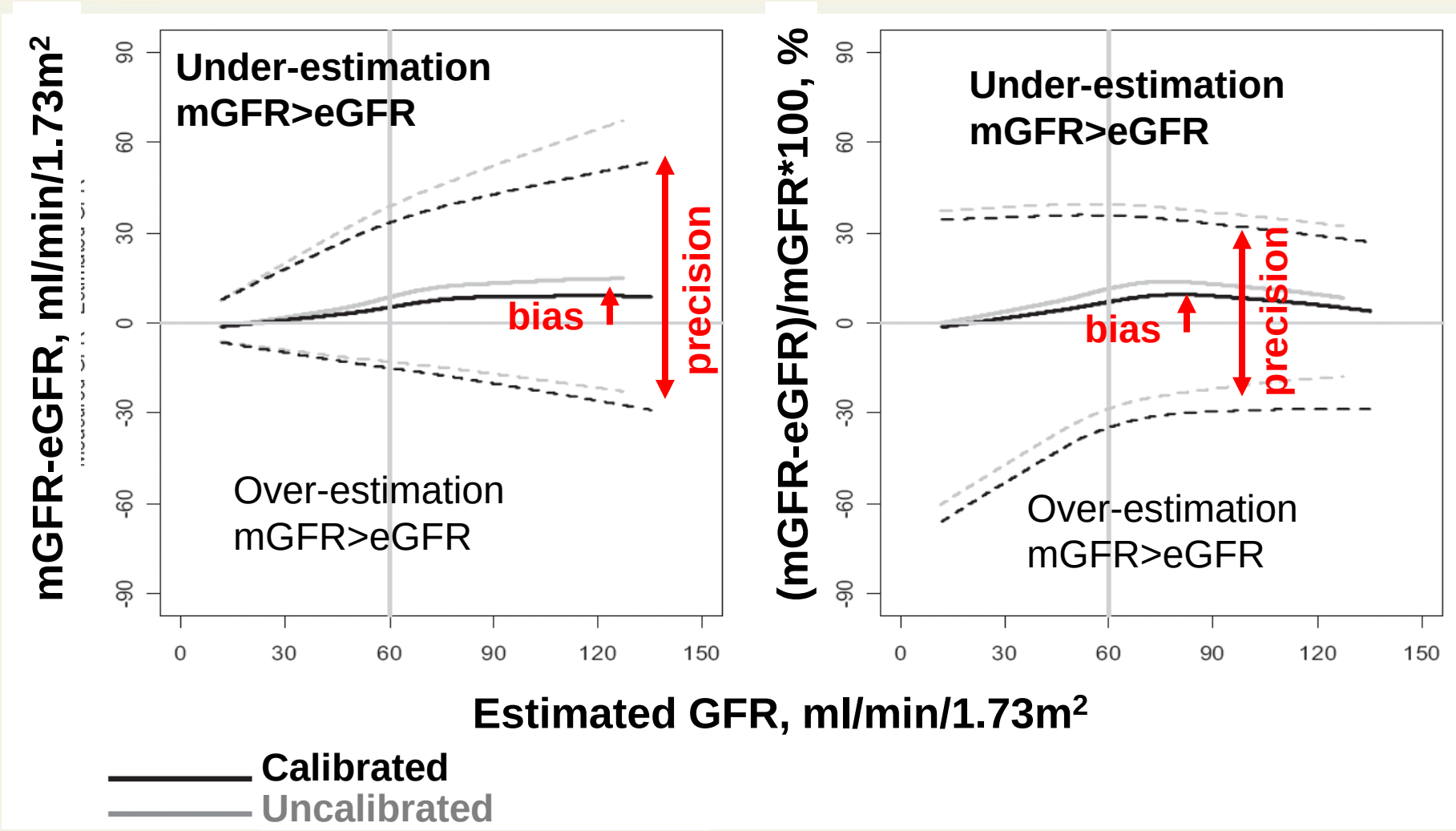
Quantifying Bias, Precision & Accuracy of Estimated GFR (eGFR) for Measured GFR (mGFR)

Criteria	Metric	Definition
Bias	Median difference Median percent difference	Median (mGFR-eGFR) Median (mGFR-eGFR)/mGFR*100
Precision	IQR difference	Interquartile range of (mGFR-eGFR)
	IQR % difference	Interquartile range of (mGFR-eGFR)/mGFR*100
Accuracy	Median absolute difference	Median |mGFR-eGFR|
	P_{30}	Percent of eGFR within 30% of mGFR
	RMSE*	Square root of mean $(\log mGFR - \log eGFR)^2$

mGFR = Measured GFR, eGFR = Estimated GFR

* RMSE measures precision when bias is 0 (development datasets)

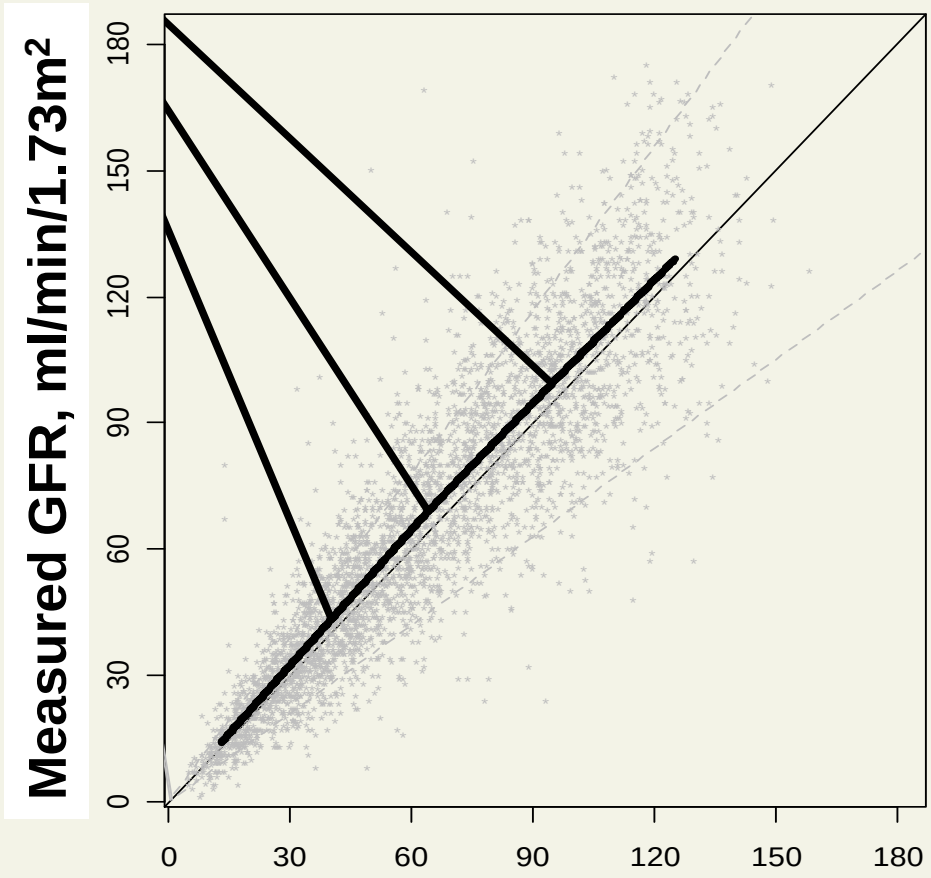
MDRD Study Equation – Creatinine Calibration



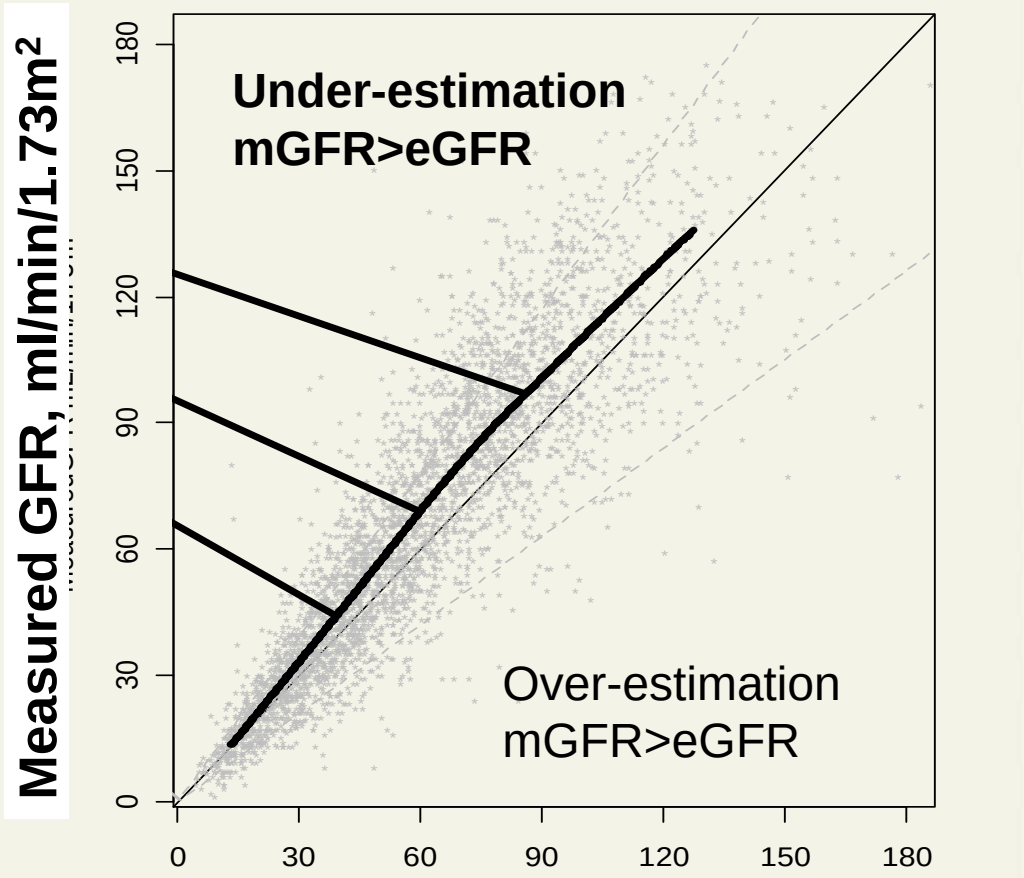
Am J Kidney Dis 2007;50:21-35

Performance of the Equations in External Validation

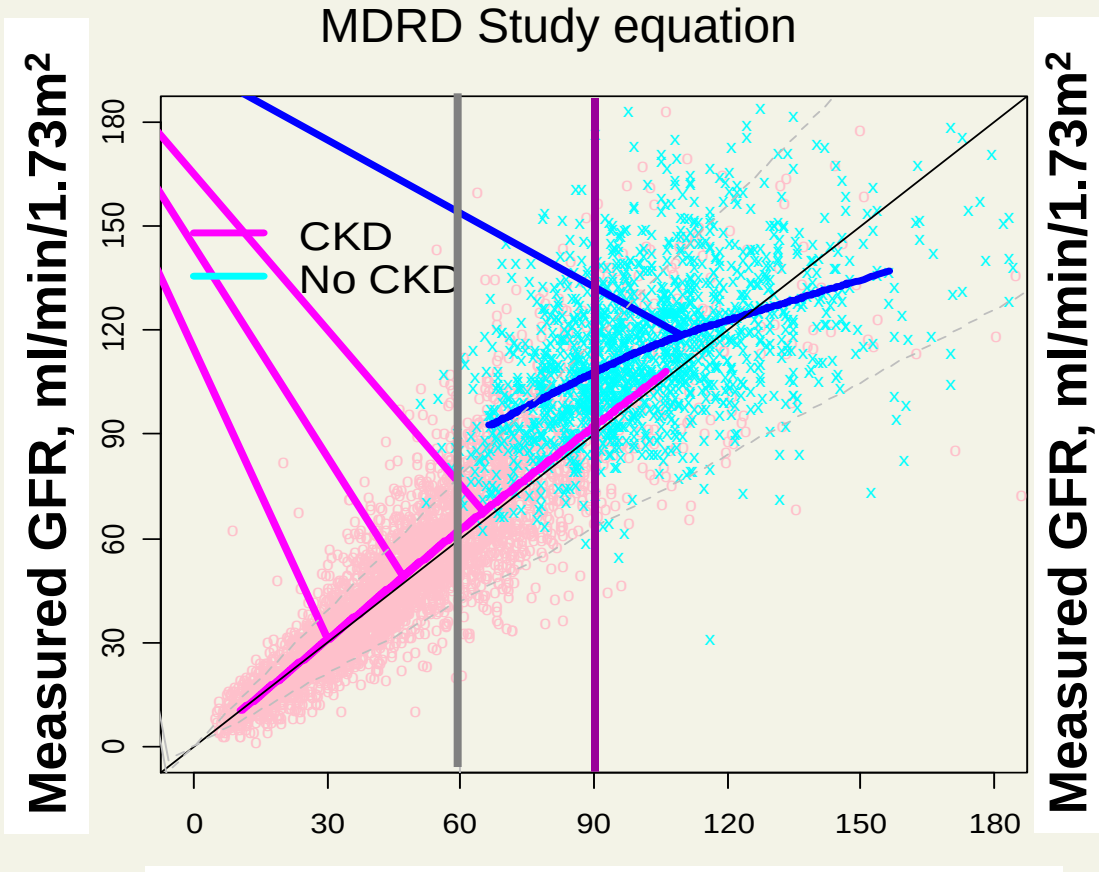
CKD-EPI A. ME SL

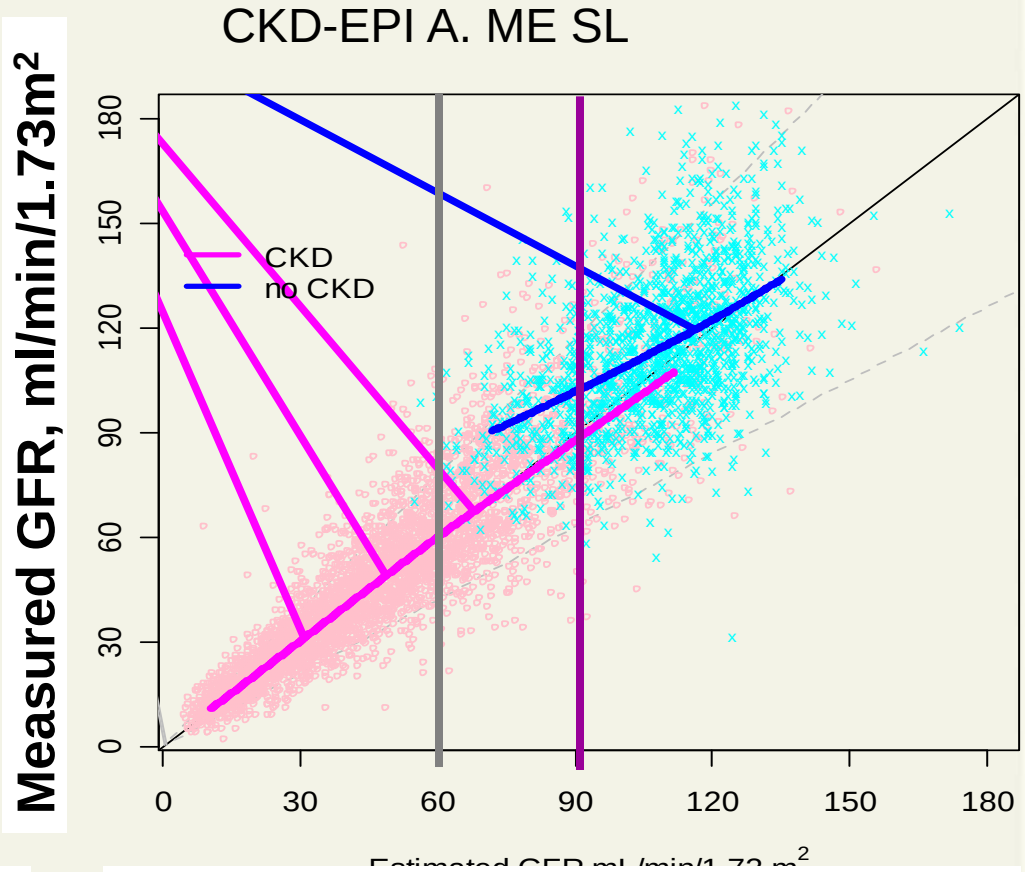


MDRD Study equation

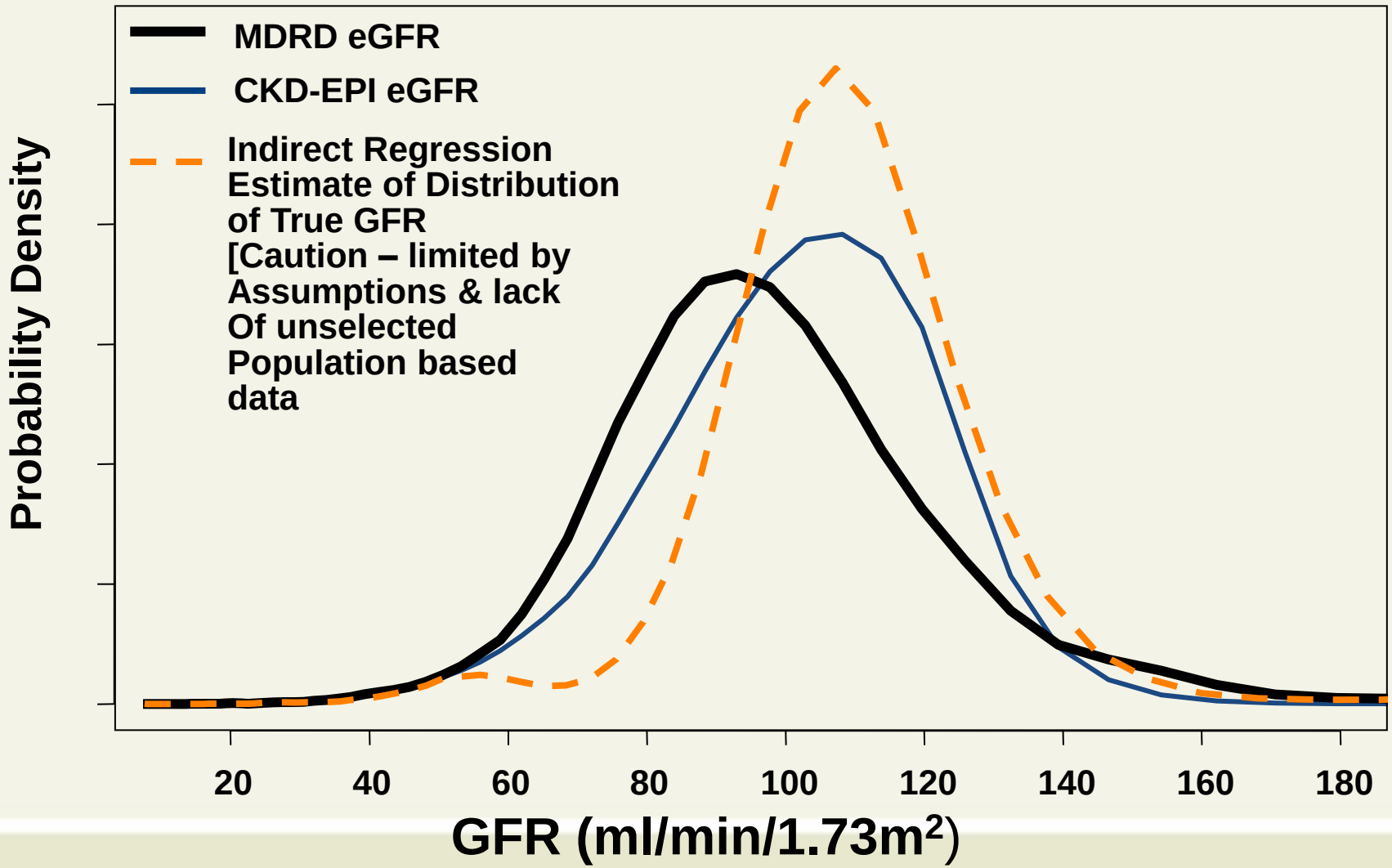


Performance of the MDRD Study equation and new CKD-EPI equation by CKD Status in the Category 2 dataset (20 studies)

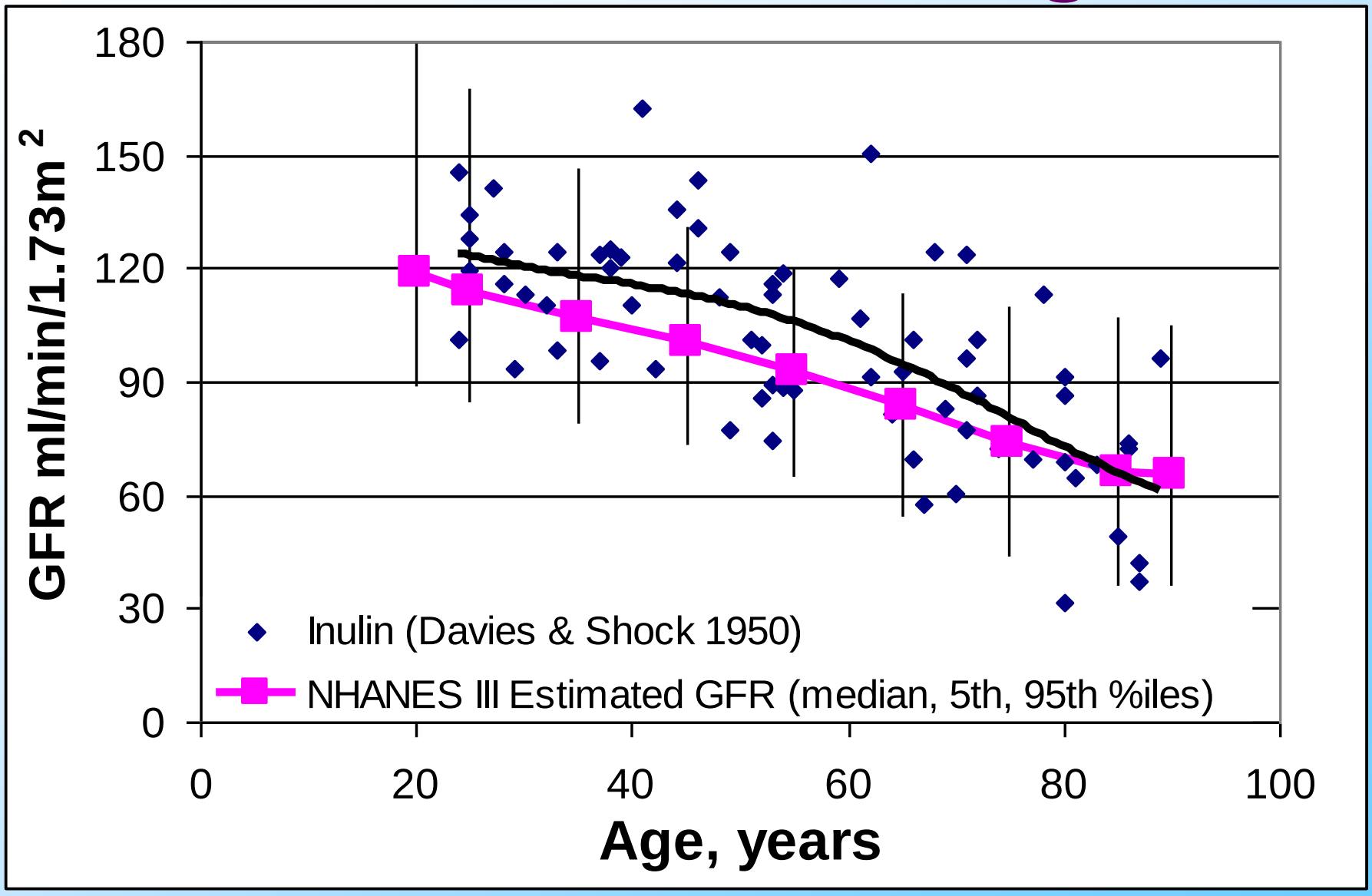




Distribution of GFR: MDRD, CKD-EPI, early estimate of "true" GFR – NHANES III



“Normal” GFR vs. Age



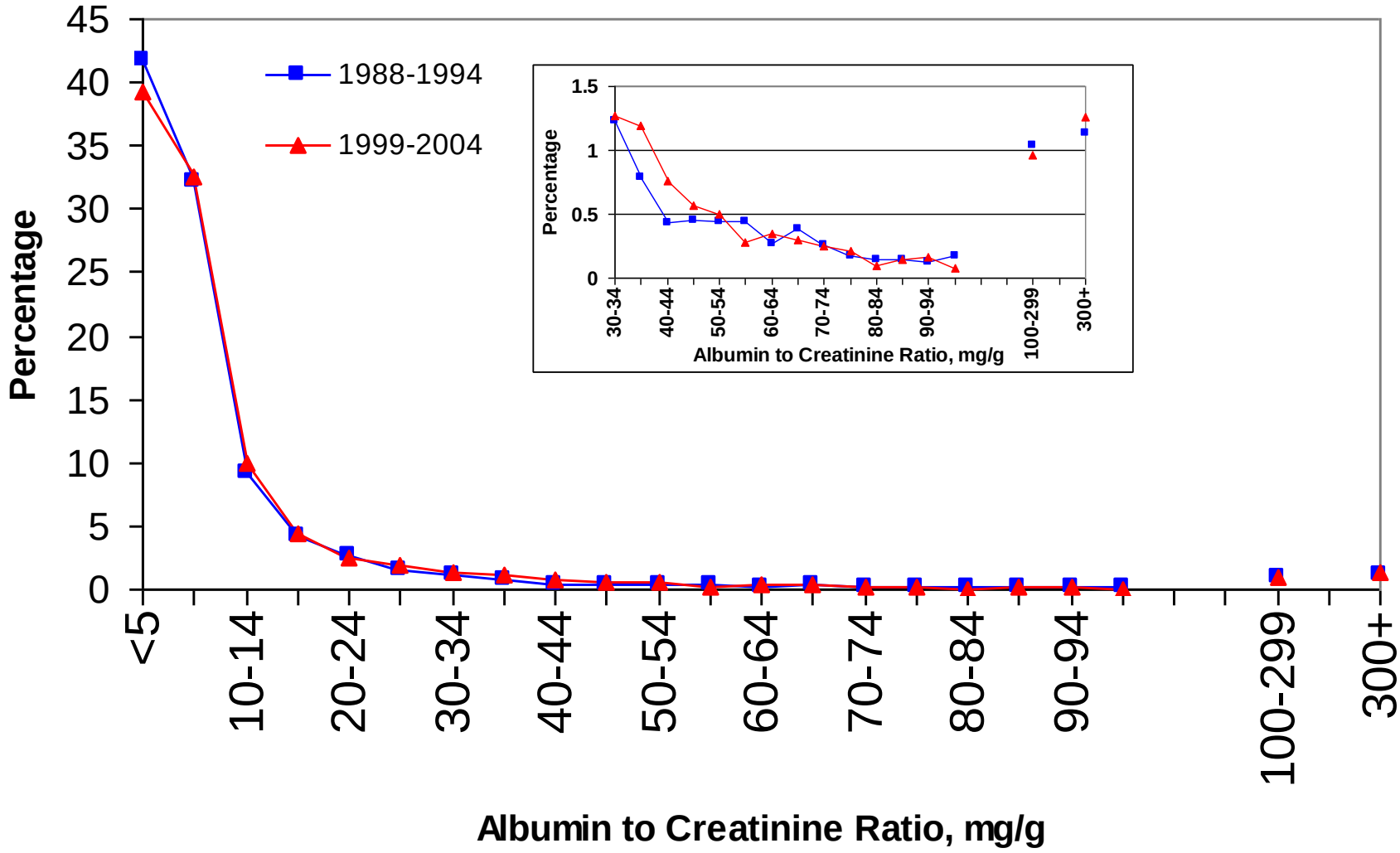
Coresh J et al. Am J Kid Dis 2003; 41: 1-12

Prevalence of Chronic Kidney Disease in the United States

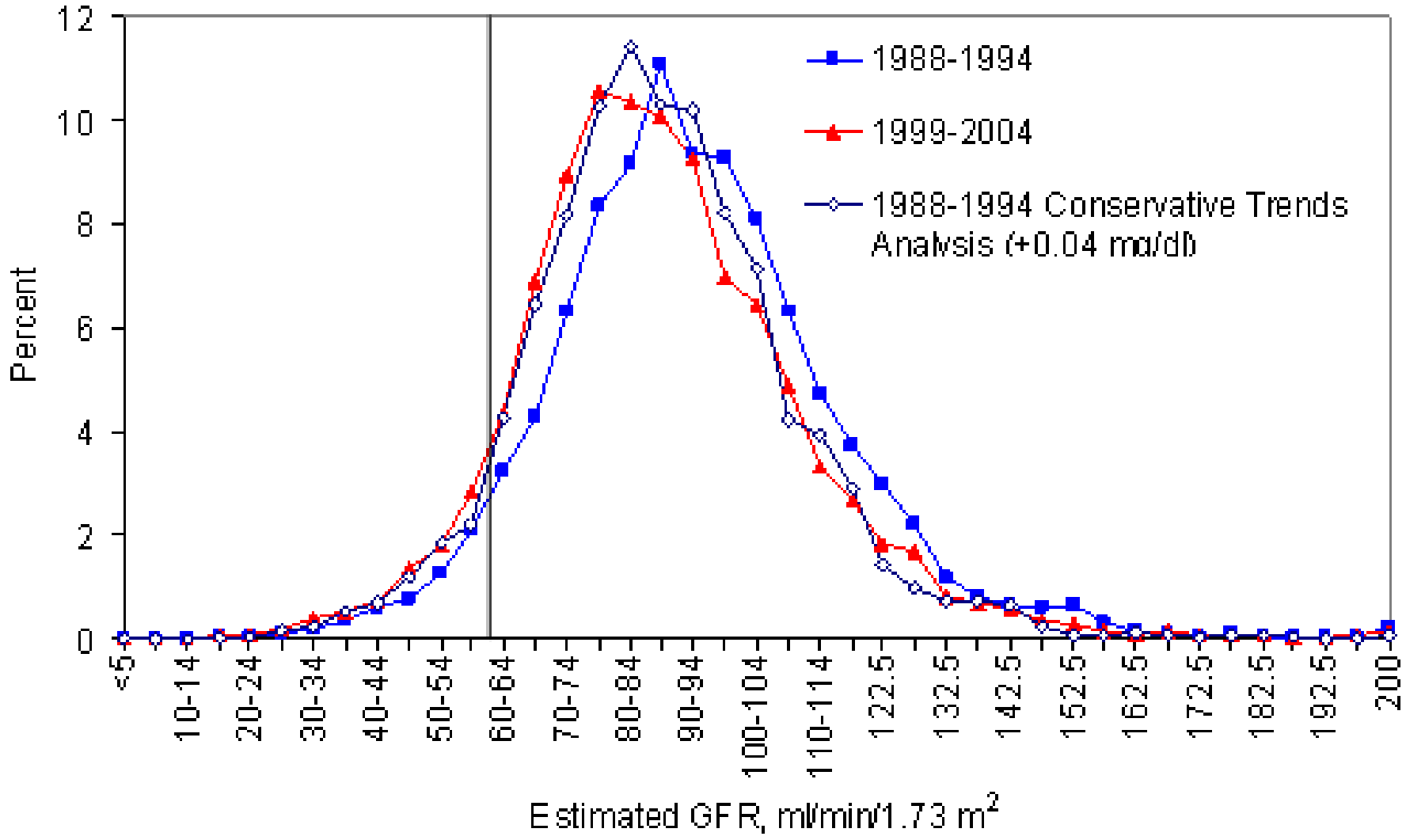
- **Design, Setting, and Participants** Cross-sectional analysis of the most recent National Health and Nutrition Examination Surveys (NHANES 1988-1994 and NHANES 1999-2004), a nationally representative sample of non-institutionalized adults aged 20 years or older in 1988-1994 (n=15,488) and 1999-2004 (n=13,233).

Coresh et al. JAMA. 2007;298(17):2038-2047

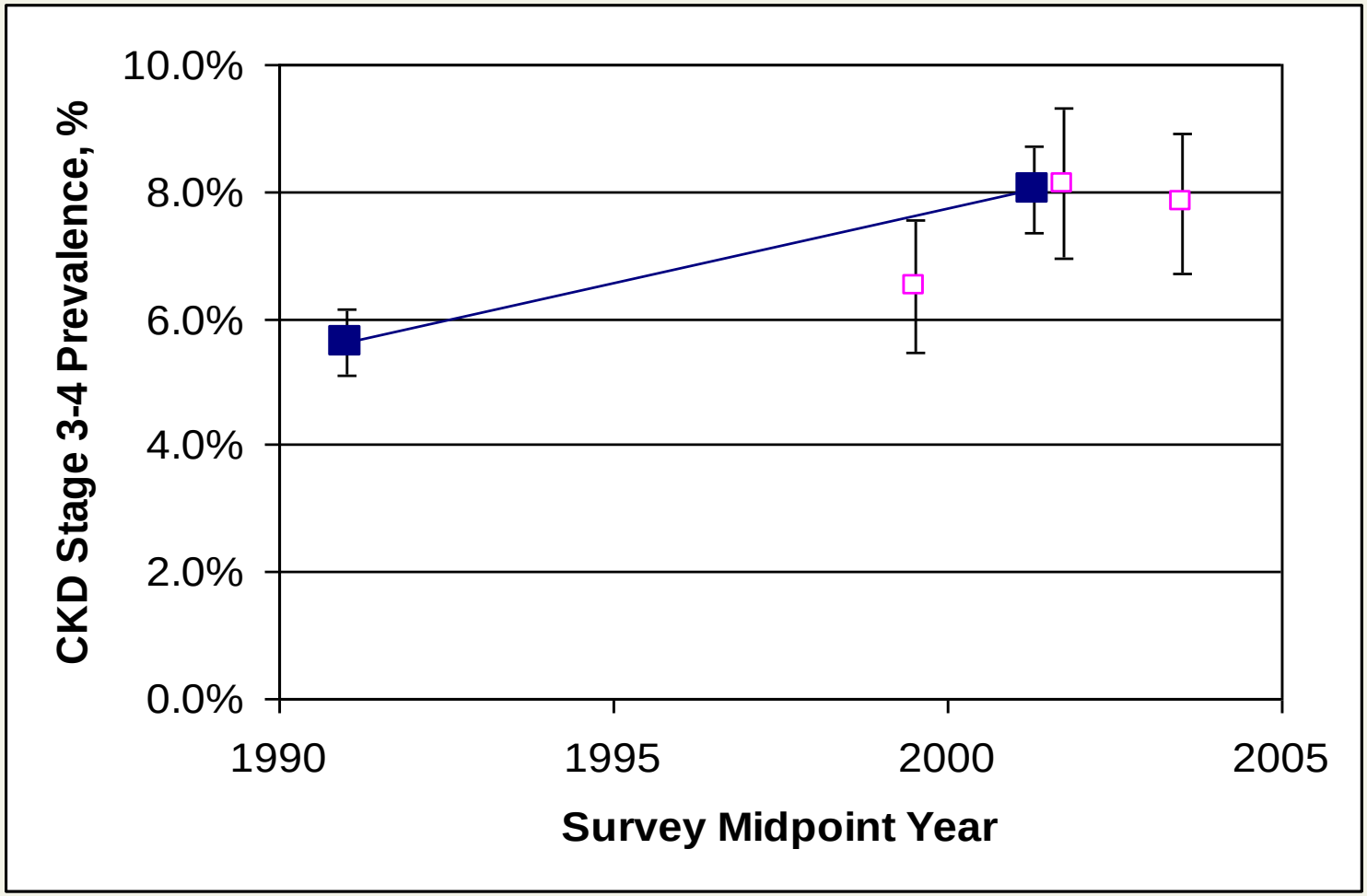
Distribution of Albumin to Creatinine Ratio



Estimated GFR Distribution

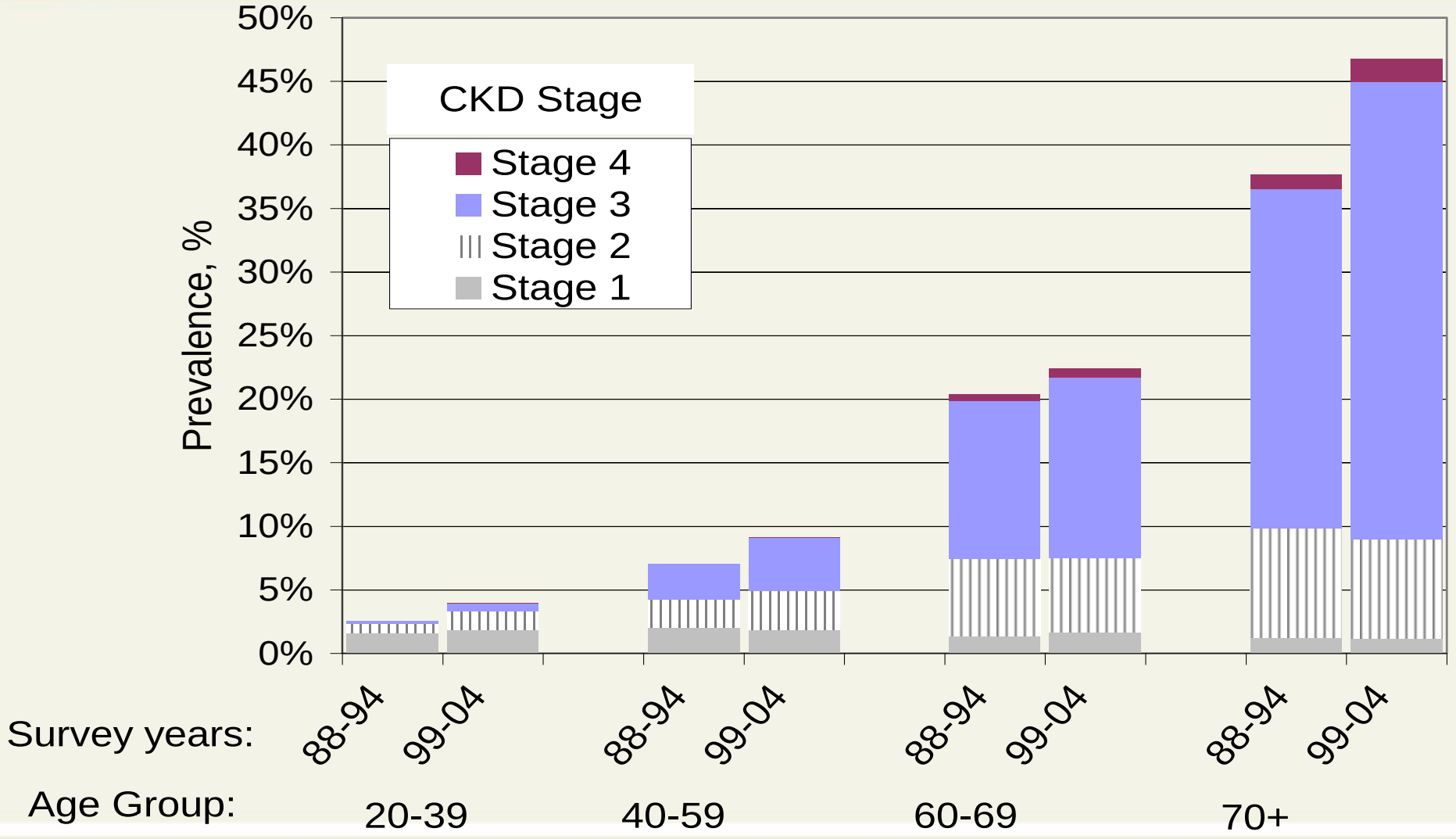


Trends in the prevalence of CKD stages 3 and 4 between NHANES 1988-1994 and 1999-2004



Empty squares denote the three component surveys in the later NHANES (1999-2000, 2001-2002 and 2003-2004). Error bars denote 95% confidence intervals.

US Trends in the Prevalence of CKD by Age and Stage



Coresh et al, JAMA in press 2007

Trends in Albuminuria 1999-2004 vs. 1988-1994

	Trends		
	OR	95% CI	P
Albuminuria in 1999-2004 vs. 1988-1994			
Unadjusted	1.18	1.03-1.34	0.01
Adjusted for age	1.15	1.00-1.32	0.05
+ sex and race	1.12	0.99-1.28	0.08
+ diagnosed diabetes and hypertension	1.06	0.93-1.21	0.39
+ body mass index	1.03	0.90-1.18	0.63

Trends in Decreased eGFR 1999-2004 vs. 1988-1994

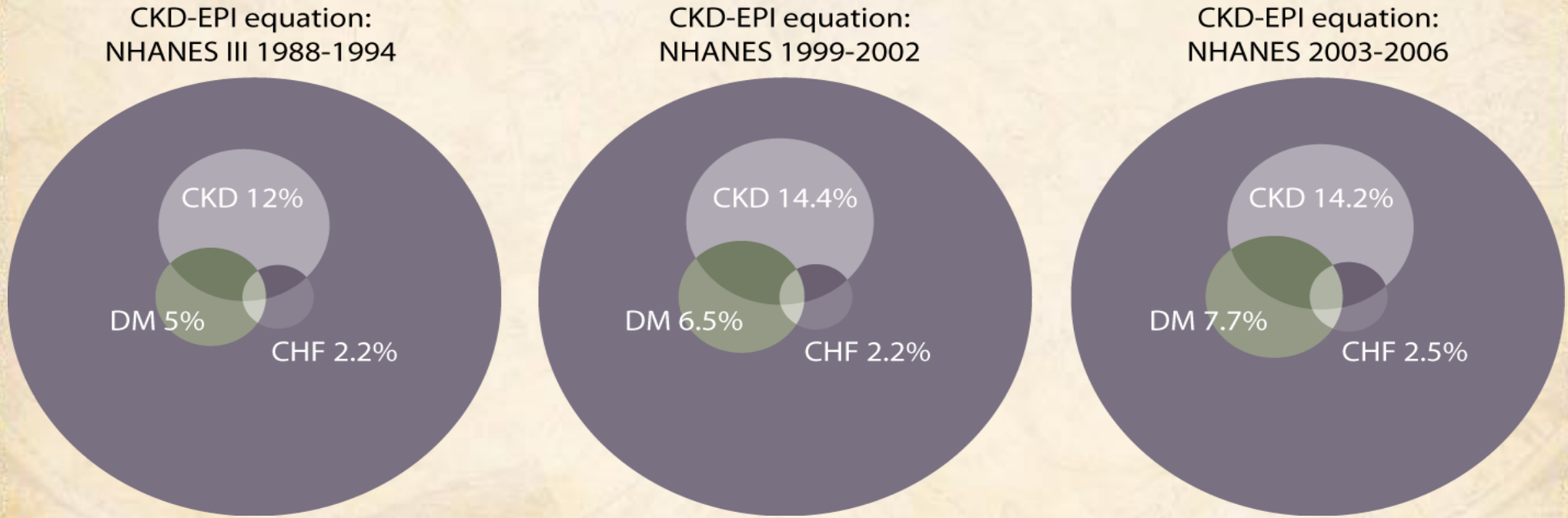
	Trends		
Estimated GFR< 60 ml/min/1.73m^2 in 1999-2004 vs. 1988-1994	OR	95% CI	P
Unadjusted	1.47	1.27-1.69	0.000
Adjusted for age	1.50	1.31-1.73	0.000
+ sex and race	1.53	1.33-1.76	0.000
+ diagnosed diabetes and hypertension	1.45	1.27-1.67	0.000
+ body mass index	1.43	1.24-1.63	0.000

Trends in Decreased eGFR 1999-2004 vs. 1988-1994 – Conservative Trends Analysis

	Conservative Trends Analysis*		
Estimated GFR< 60 ml/min/1.73m^2 in 1999-2004 vs. 1988-1994	OR	95% CI	P
Unadjusted	1.17	1.02-1.34	0.03
Adjusted for age	1.13	0.99-1.30	0.07
+ sex and race	1.15	1.00-1.32	0.05
+ diagnosed diabetes and hypertension	1.10	0.96-1.26	0.17
+ body mass index	1.08	0.94-1.24	0.29

Distribution of NHANES participants with diabetes, congestive heart failure, & markers of CKD, with GFR estimated by the CKD-EPI equation

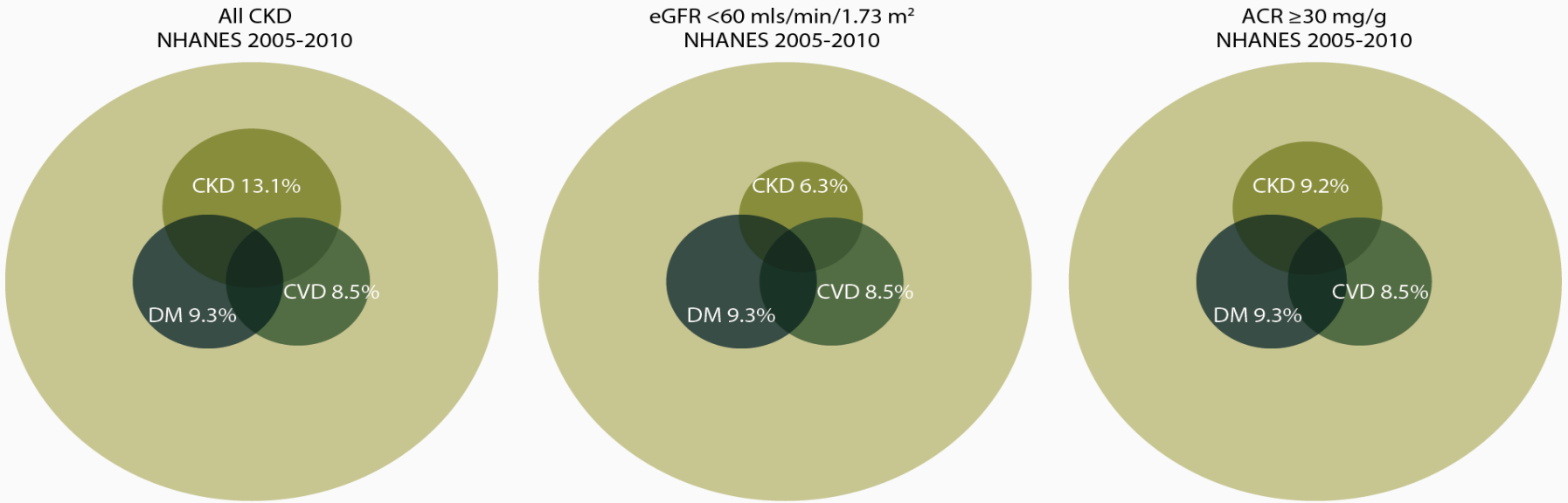
Figure 1.1 (continued; Volume 1)



NHANES participants age 20 & older.

Distribution of NHANES participants with diabetes, congestive heart failure, & markers of CKD, 2005–2010

Figure 1.1 (volume 1)



NHANES participants 2005–2010, age 20 & older; eGFR calculated using CKD-EPI equation; urine albumin creatinine ratio (ACR).

CKD: Associated Conditions & Consequences of Under-diagnosis & Inaction

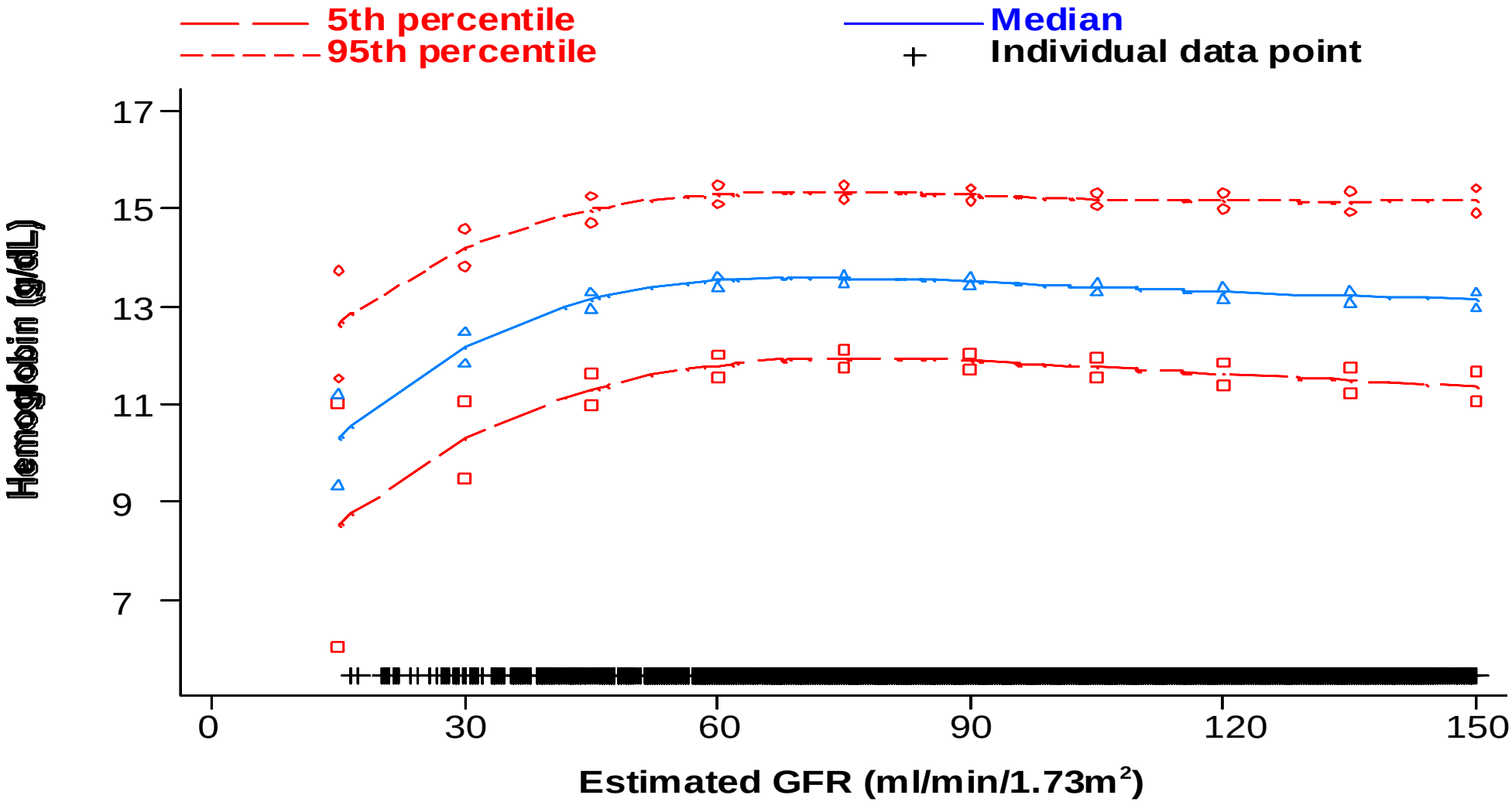
Association of Complications with level of GFR in Adults

	Guideline
• Hypertension	#7
• Anemia	#8
• Nutrition	#9
• Abnormalities of bone, calcium & phosphorus	#10
• Neurological changes	#11
• Functioning and Well Being	#12

Am J Kid Dis 39:S1-S266, 2002

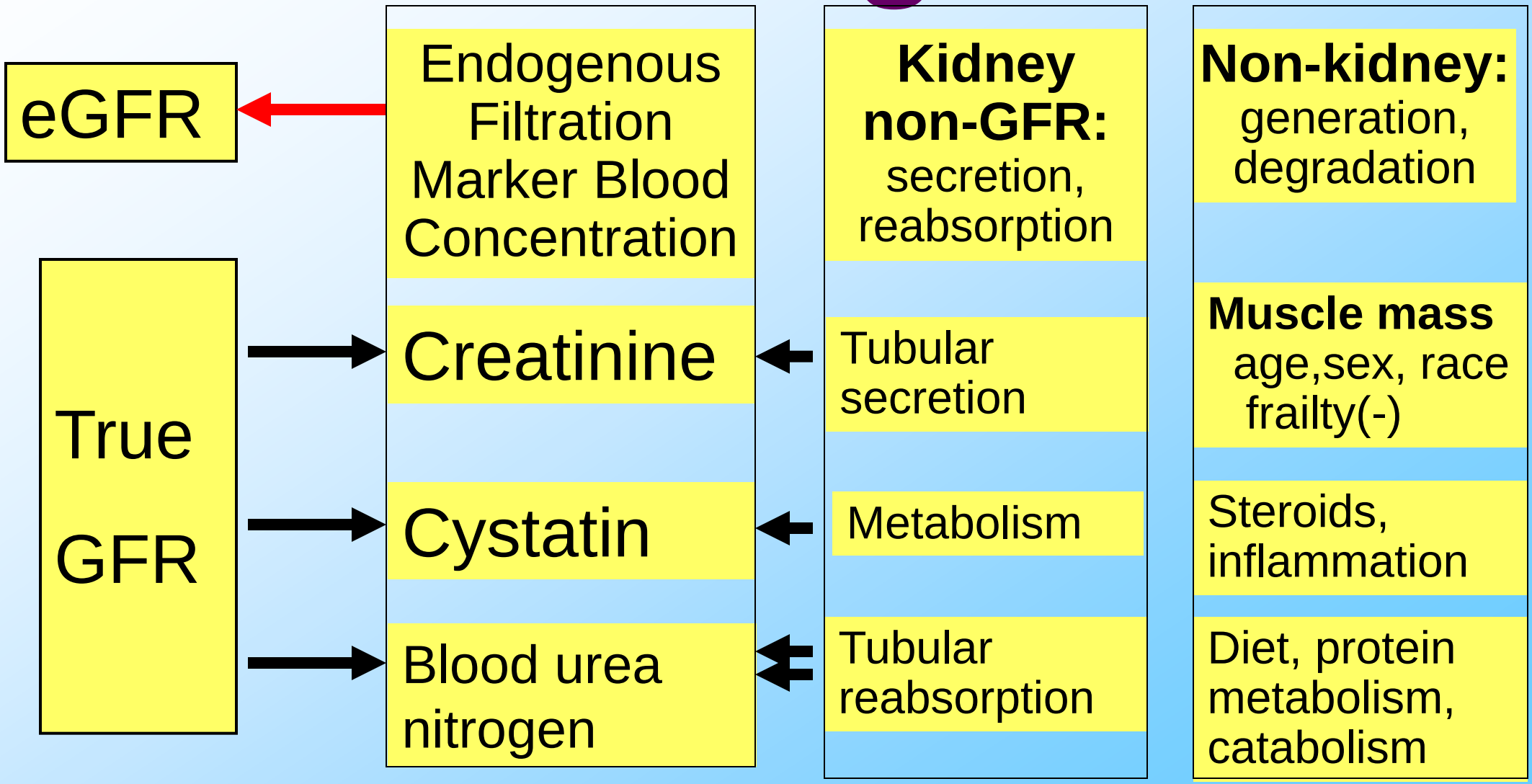
Hemoglobin Levels, Women

Median and 5th and 95th Percentiles, adjusted to age 60 years



Astor B et al. Arch Int Med 2002; 162:1401-1408

Estimating GFR



Risk Factors for ESRD & CKD

MULTIPLE RISK FACTOR INTERVENTION TRIAL (MRFIT)

- **Randomized trial to test effect of a multifactor program to prevent CHD**
- **361,662 men screened from 11/73-11/75**
- **Screening took place in 18 U.S. cities**
- **12,866 high risk men, 35-57 years, entered into trial**

MRFIT SCREENEES (N=361,662) DATA COLLECTED

- Age, race*, sex
- History of MI
- Prescribed medication for diabetes*
- Blood Pressure*
- Serum cholesterol-
- Cigarette smoking-
- Zip code

Red indicates published ESRD risk factors

* Indicates ESRD relationship is STRONGER than for CHD; - indicates WEAKER

METHODS

Outcome

-ESRD incidence (treated or death from renal disease) ascertained from the National Death Index (1979 to 1990) and the Social Security Administration (1973 to 1990)

Analysis

-Survival analysis using Kaplan-Meier and Cox proportional hazards analysis

NUMBER OF ESRD CASES IN MRFIT SCREENEE MEN THROUGH DECEMBER, 1990

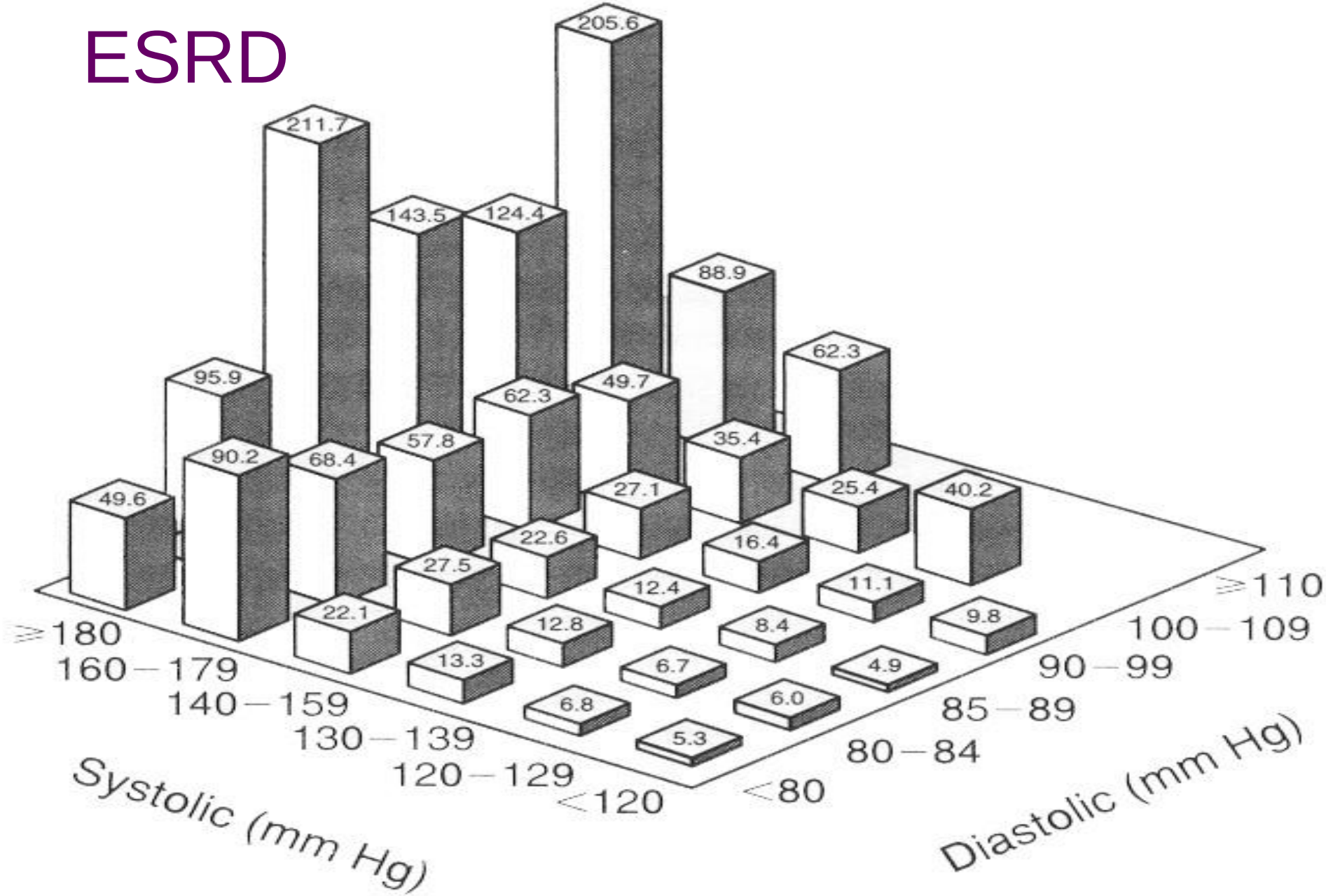
		ESRD		
	No. Men	Treated	Deaths	Total
Ethnic Group				
White	317,908	553	128	681
Black	23,490	117	38	155
Other	12,618	38	13	51
Total	353,337	708	179	887

RELATIVE RISK OF ESRD IN 20,222 AFRICAN AMERICAN MEN COMPARED WITH 332,544 WHITE MEN SCREENED FOR MRFIT, 1973-90

Adjusted for	All-Cause ESRD	Hypertensive ESRD
Age only	3.20 (2.62-3.91)	5.16 (3.64-7.31)
Age, systolic blood pressure	2.56 (2.09-3.13)	3.84 (2.68-5.48)
Age, serum cholesterol	3.25 (2.66-3.98)	5.21 (3.68-7.40)
Age, cigarettes/d	3.26 (2.67-3.98)	5.35 (3.77-7.59)
Age, median income	2.32 (1.82-2.95)	2.83 (1.80-4.45)
Age, diabetes	2.73 (2.23-3.34)	4.83 (3.40-6.86)
Age, previous myocardial infarction	3.20 (2.62-3.91)	5.19 (3.66-7.35)
All of the above	1.87 (1.47-2.39)	2.42 (1.52-3.84)

Klag et al. JAMA, 1997

BP & Risk of ESRD



Mid-Atlantic ESRD Case-Control Study

- **Investigators**: Perneger TV (Phd thesis), Klag MJ, Whelton PK
- **Objective:** To systematically study risk factors for ESRD
- **Design:** Case-control study.
- **Setting:** Population-based study in Maryland, Virginia, West Virginia, and Washington, D.C.
- **Participants:**
  - 716 newly treated patients with kidney failure aged 20 to 64 years identified using ESRD registry records
  - 361 controls selected by random digit dialing and frequency age-matched
- **Measurements:** Self-reported history by telephone interview

Risk Factors for ESRD in Mid-Atlantic Case Control Study

- h/o hypertension (presence & duration)
- h/o diabetes (not only for diabetic kidney disease)
- African-American race
- Low income
- Poor access to care (number of mising teeth)
- Analgesic use (acetominophen)
- Alcohol consumption (>2 drinks/day)
- Family history of ESRD
- h/o MI or stroke
- Recreational drug use
- Smoking (abstract only)

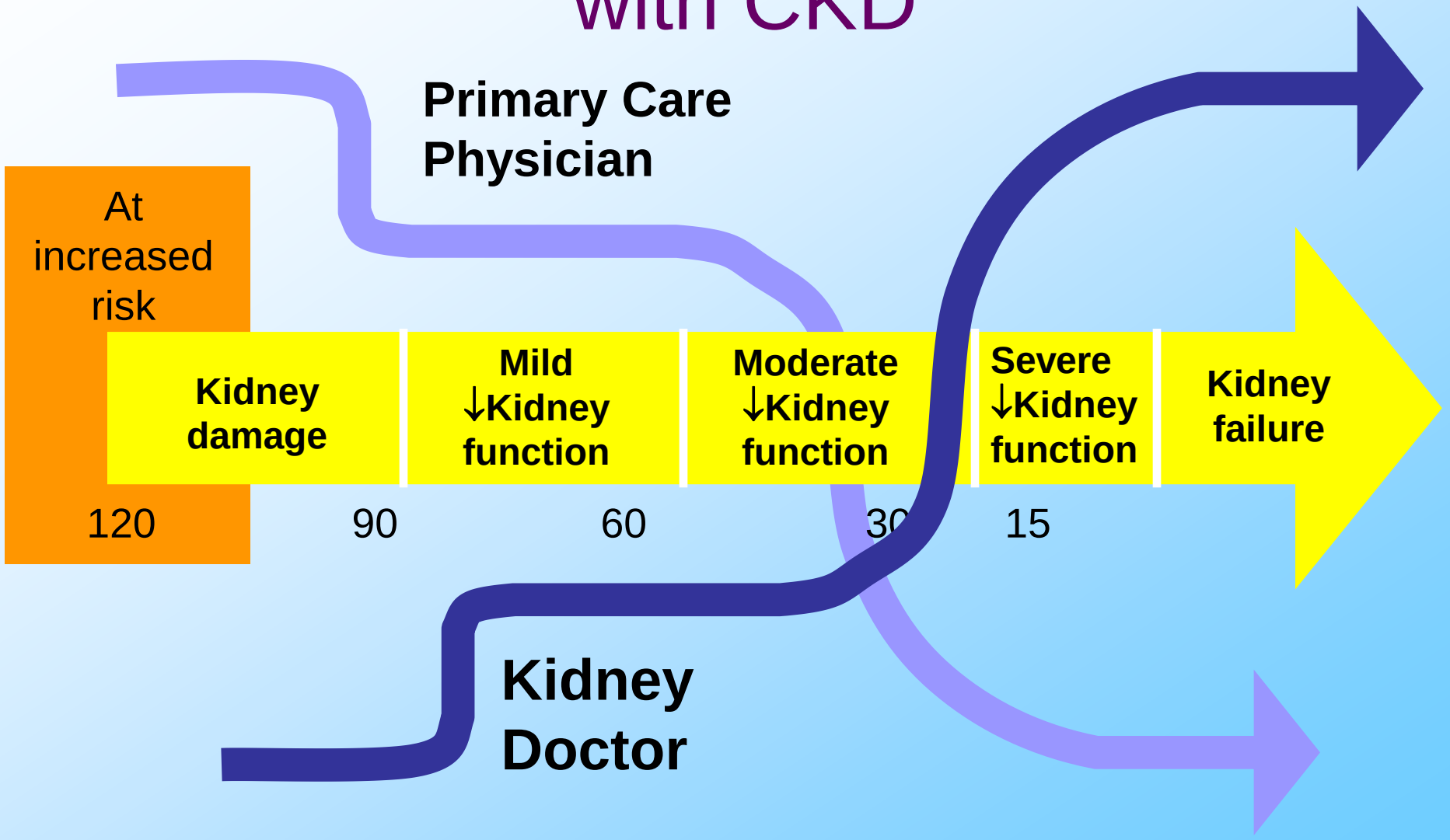
Summary

- **In adults Chronic Kidney Disease (CKD) is far more common than ESRD**
  - **15 million (8%) adults with CKD stage 3-5 (GFR<60 ml/min/ 1.73 m^2)**
  - **~10 million (5%) other adults with kidney damage (persistent proteinuria)**
- **CKD is associated a number of treatable conditions**

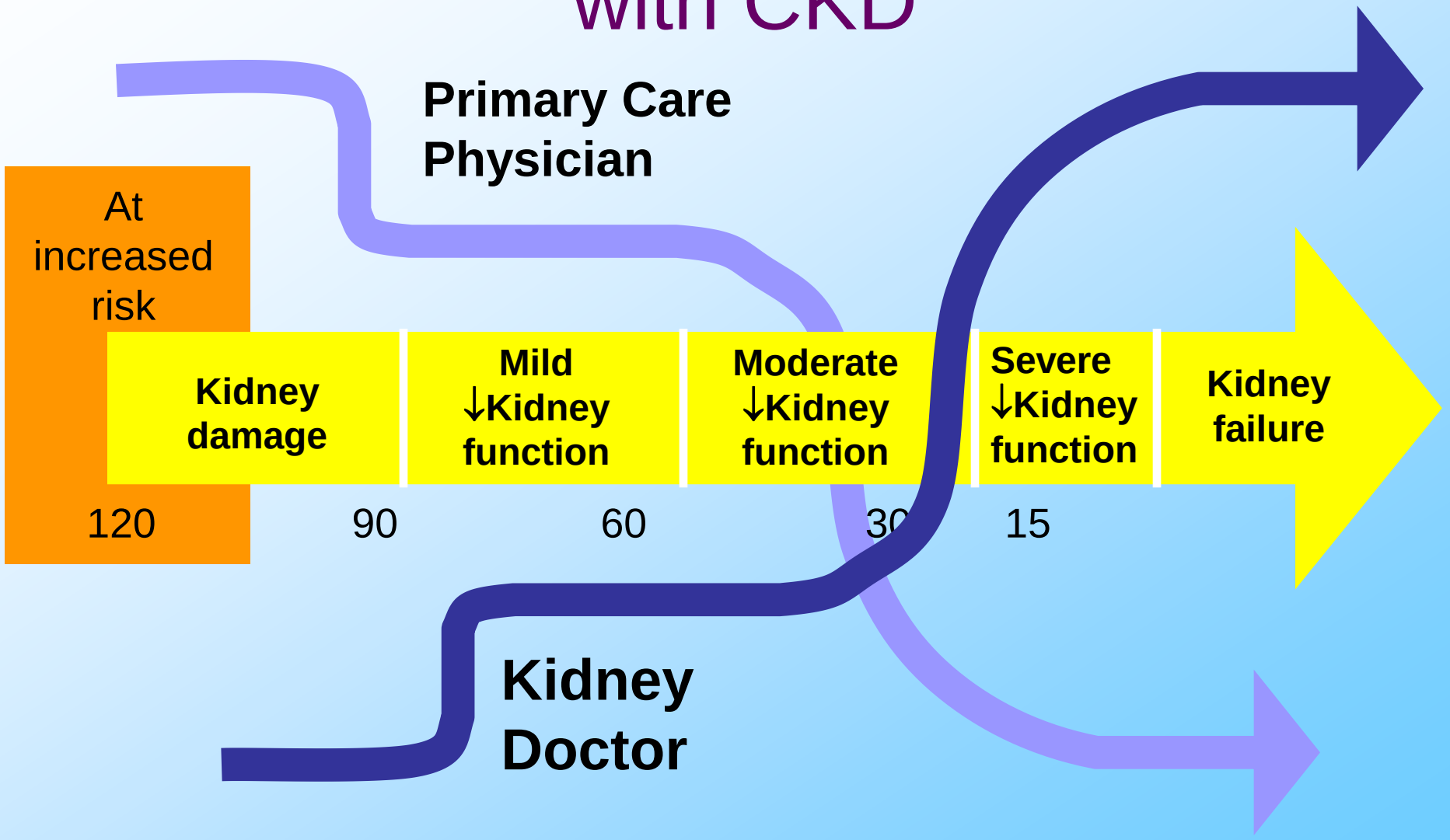
Key Points

- ESRD is treated kidney failure which reflects both treatment (good) and failure (bad)
- CKD & CVD share many risk factors and mechanisms (endothelial damage, inflammation…)
- Trends in CKD (increasing→ flat) differ from trends in CVD (most risk factors except obesity, DM are decreasing)
- CKD patients have additional risk factors for CVD (including anemia and volume overload) which play a smaller role in the general population

Co-Management of Pts with CKD



Co-Management of Pts with CKD



EXTRA SLIDES

	Chronic kidney disease	Acute kidney injury
Definition		
Functional criteria	GFR <60 mL/min per 1·73 m² for >3 months	Increase in serum creatinine by 50% within 7 days; increase in serum creatinine by 26·5 µmol/L (0·3 mg/dL) within 2 days; or oliguria
Structural criteria	Kidney damage for >3 months (albuminuria is the most common marker of kidney damage and is also associated with rapid progression)	None
Staging	GFR categories (mL/min per 1·73 m²) and related terms†: G1 ≥90 (normal or high); G2 60–89 (mildly decreased‡); G3a 45–59 (mildly to moderately decreased); G3b 30–44 (moderately to severely decreased); G4 15–29 (severely decreased); G5 <15 (kidney failure) Albuminuria categories, approximate equivalent for AER (mg per day) and ACR (mg/g) and related terms: A1 <30 (normal to mildly increased); A2 30–300 (moderately increased‡); A3 >300 (severely increased‡)	Stages based on serum creatinine or urine output; stage 1: serum creatinine ≥1·5–1·9 times baseline, ≥26·5 µmol/L increase, or urine output <0·5 mL/kg per h for 6–12 h; stage 2: serum creatinine ≥2·0–2·9 times baseline or urine output <0·5 mL/kg per h for ≥12 h; stage 3: serum creatinine ≥3·0 times baseline, ≥353·6 µmol/L (≥4 mg/dL), renal replacement therapy, or (in patients <18 years) a decrease in estimated GFR to <35 mL/min per 1·73 m², urine output <0·3 mL/kg per h for ≥24 h, or anuria for ≥12 h
Burden*		
Prevalence	~10% of adults (from 4% at 20–39 years to 47% at ≥70 years in the USA)[6,8,37,38]	Not applicable for a short-term illness (history of acute kidney injury of any severity present in 45% at chronic kidney disease stage ≥4)[39]
Annual incidence	~1% in middle age; twice as frequent in black compared with white populations[40–42]	Acute kidney injury requiring hospital admission in Alberta, Canada for patients without chronic kidney disease 0·1% (0·01% requiring dialysis); for patients with stage 3 disease 0·5–7·1% (0·03–0·17%); for patients with stage 4 disease 7·0–11·7% (0·5–2·5%); and 34·8% for acute kidney injury of any severity in chronic kidney disease stage ≥4[39,43] For patients already admitted to hospital, rates are ~10–20% for any acute kidney injury with 0·3% requiring dialysis (highest with sepsis, cancer and surgery)
Lifetime cumulative incidence	~50% for chronic kidney disease[44] and ~2% in white and ~7% in black populations for end-stage renal disease[45,46]	..

GFR=glomerular filtration rate. AER=albumin excretion rate. ACR=albumin-to-creatinine ratio. *Varies by age and risk factor distribution. †In the absence of evidence of kidney damage, GFR category G1 or G2 do not fulfil the criteria for chronic kidney disease. ‡Terms for categories G2 and A2 are relative to young adult levels; category A3 includes nephrotic syndrome (albumin excretion usually >2200 mg/day [ACR >2220 mg/g]).

Table 1: **Definitions, stages, and burden of chronic kidney disease and acute kidney injury**

The Lancet; 382:158 - 169, 13 July 2013