Chronic Kidney Disease – A Window into Understanding Health Disparities

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Overview

- Case illustrating racial/ethnic disparities in kidney disease
- A premise about disparities as a focal point in science and medicine
- Definitions & framework for understanding disparities
- Science of disparities
  - Why kidney disease occurs more often in minorities
  - Glimpse of my research and others

A Patient

- **Chief Complaint:** 46 year old African American male presents to Emergency Room for generalized weakness, nausea and vomiting
- **History of Present Illness:** Increasing lower extremity edema for 2 months. Seen by private physician (primary care physician of his mother). No lab work done, but placed on furosemide. Edema improved, but worsening weakness with 15 pound weight loss over 2 months. Presented to Emergency Room with nausea and vomiting of 3 days duration
- **Past Medical History:** No diagnosis of kidney disease; no other significant past history (no HTN, DM, CVD)
- **Family History:** Diabetes and Hypertension run in family
- **Medications:** No prescription or over the counter meds

A Patient

- **Physical Examination:** Chronically ill appearing young man in no acute distress

  T 97.4F; HR 96; RR 16 BP 141/76; O2 Saturation: 99% (room air)

  HEENT: pale conjunctiva, no icterus, no JVP

  lungs clear, CV exam within normal limits, abdomen soft, nontender, nondistended, remainder of exam normal.
- **Laboratory findings:** Na 137, K 4.4, bicarbonate 19, chloride 90, AG 28, calcium 5.8, phos 13, BUN 240, creatinine 28
- **Hospital Course:** Admitted, seen by nephrology service. Temporary catheter placed, hemodialysis started on admission.

Key features

- African American patient with kidney failure
- Late presentation for care
- Poorly prepared for kidney failure
- Urgent initiation of hemodialysis possibly limiting optimal treatment

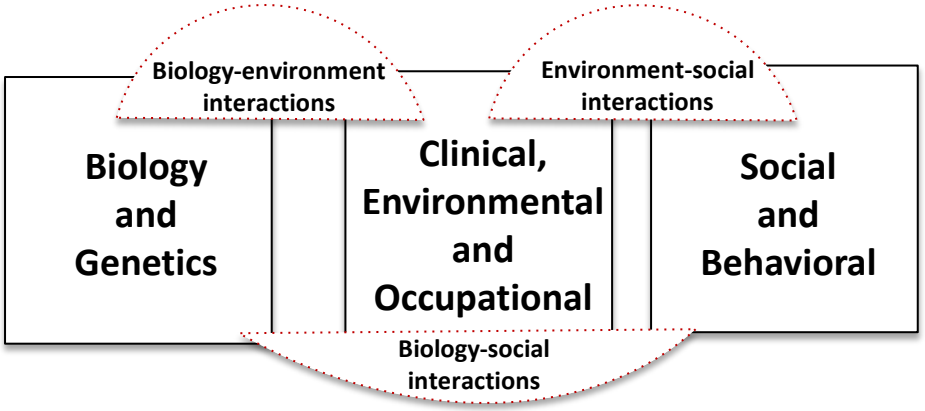
Premise

Science on disparities …

clinical care with diverse patients…

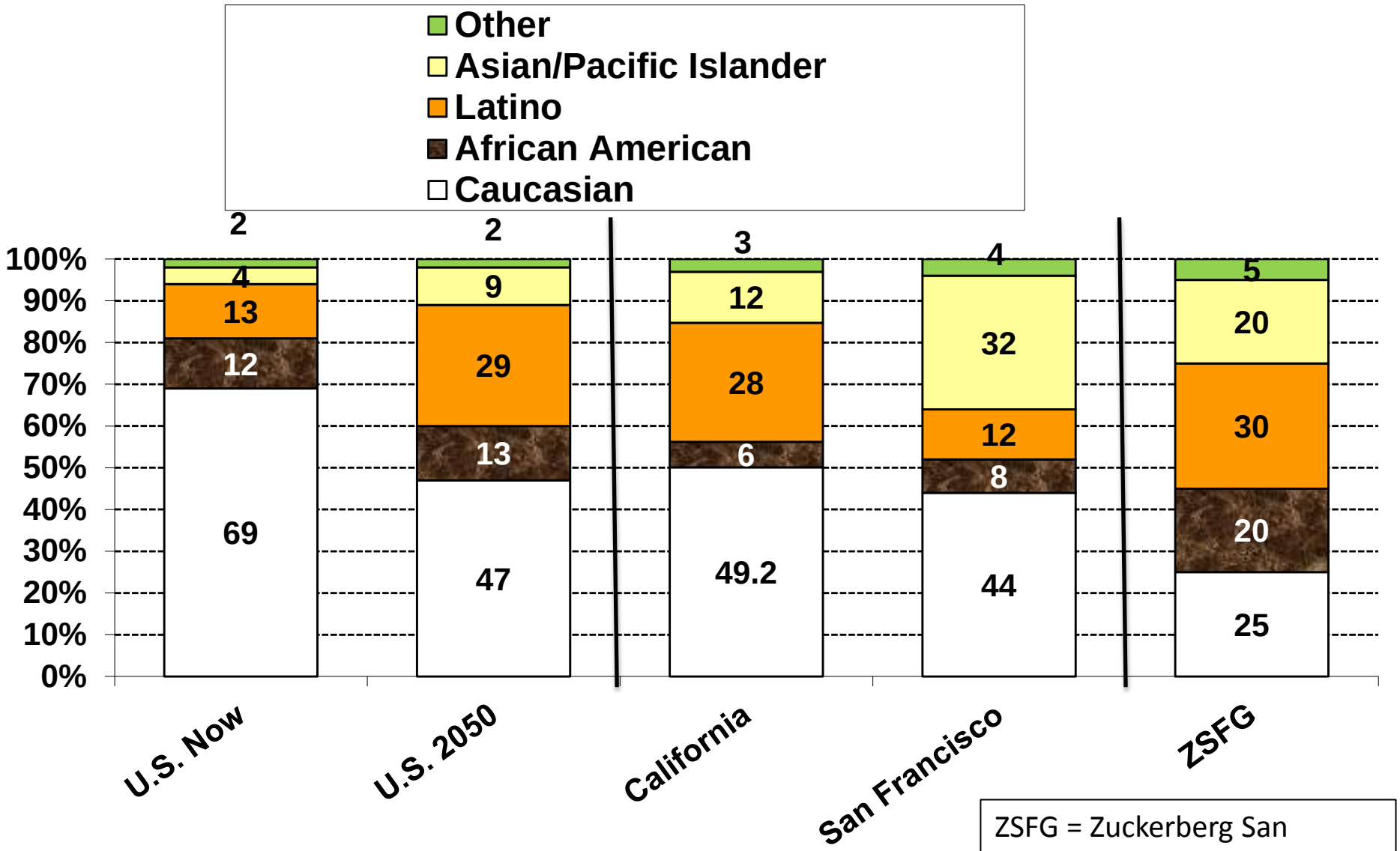
and education about disparities…

enhances all of Medicine and human health.



Learning about disparities allows the examination of complex interactions that contribute (often unequally for different clinical problems) to human health

Race/Ethnic Composition
United States, California and ZSFG



ZSFG = Zuckerberg San Francisco General Hospital

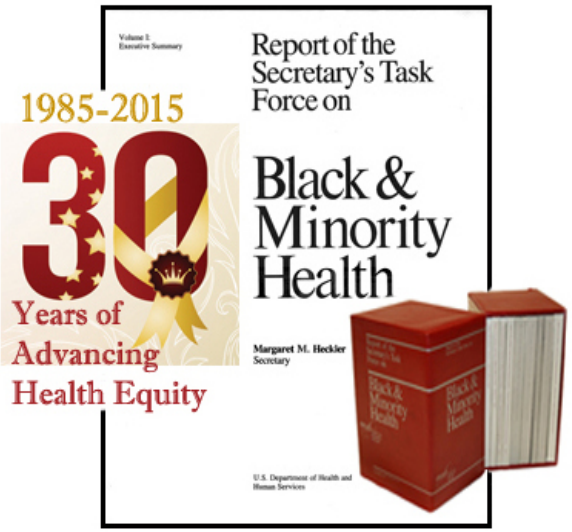
2015 - A Year of Anniversaries

December 1, 1955

- Rosa Parks changed the course of history and inspired us all

September 1985

- US Dept of Health and Human Services landmark Heckler report
- Documented health disparities among racial and ethnic minorities
- Disparities are *"an affront both to our ideals and to the ongoing genius of American medicine."*
- Served as driving force for ending health disparities and advancing health equity in America



Disparities: What do we mean?

- Disparity (dis per'ə tē) ***n***. a difference or lack of **equality**/ --pl. –ties
- Health Care should be:
  - Safe
  - Effective
  - Patient centered
  - Timely
  - Efficient
  - **Equitable** = providing care that does not vary in quality because of personal characteristics such as gender, ethnicity, geographic location or socio-economic status

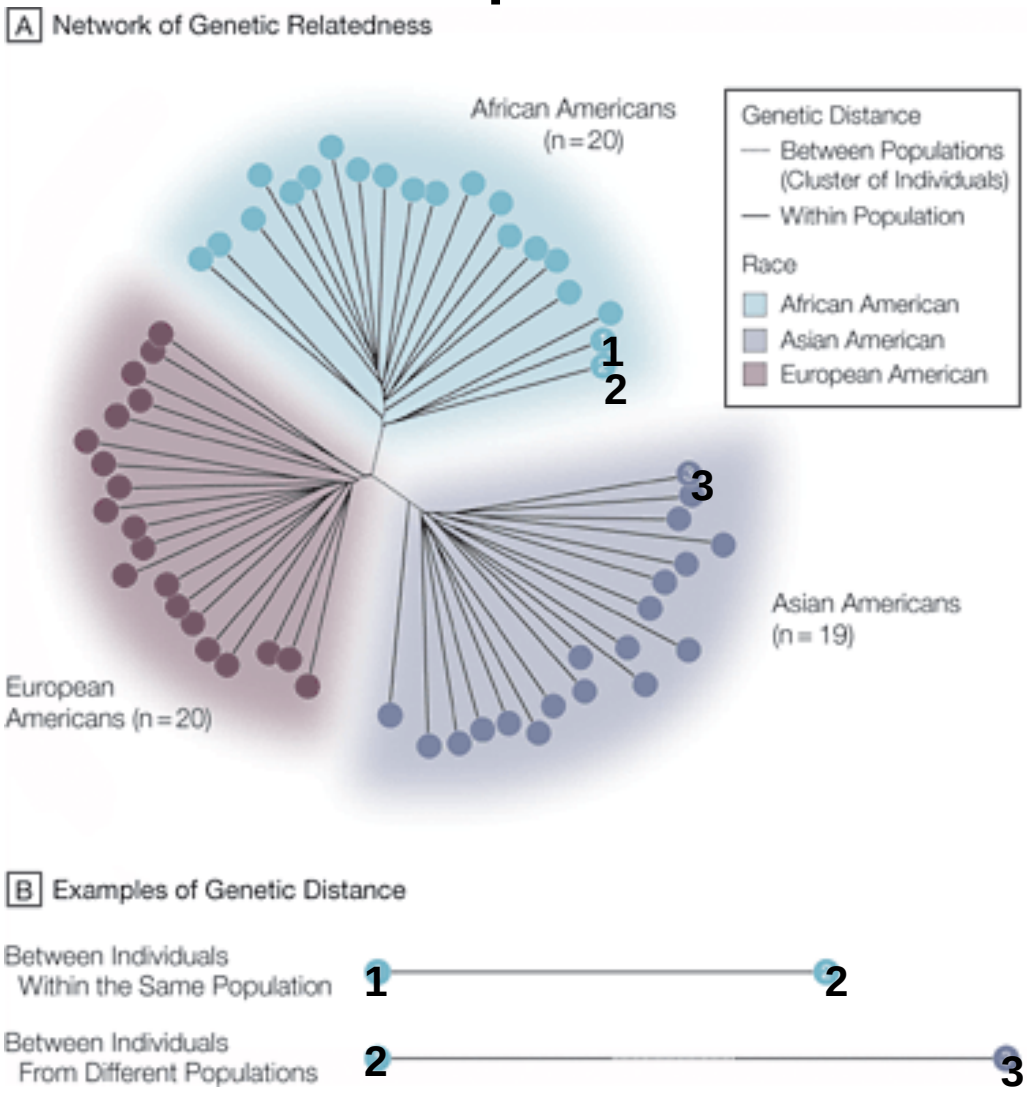
Institute of Medicine

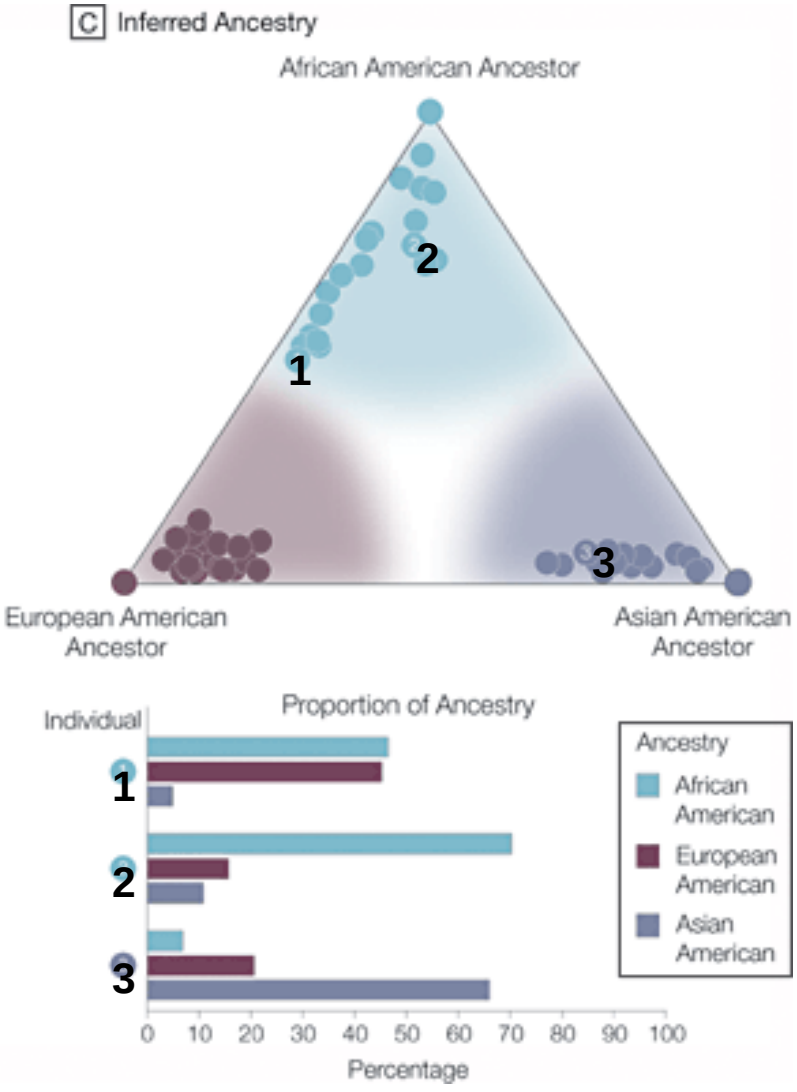
Race: What do we mean?

- Race (rās) ***n***. a group of people united or classified together on the basis of common history, nationality, or geographic distribution

  Webster's New World Dictionary, Revised Edition, 1996
- "a construct of human variability based on perceived differences in biology, physical appearance and behavior",-- not a biological reality. *Institute of Medicine, United States*
- "Information about genetic group membership captured by notions of race is, in general, less than that obtained by making inferences of ancestry from geographic or explicit genetic data" *Bamshad M.*

Inference of Individual Ancestry Proportions From Genetic Data





Bamshad, M. JAMA 2005;294:937-946.

Non-uniformity of ***health*** among racial and ethnic groups is extensively documented

- *Life expectancy at birth* – Blacks vs. Whites, 10 year gap for men, 5 year gap for women
- *Infant mortality rate* – Blacks and Native Americans twice as high vs. Whites.
- *Death rate* – Blacks vs. whites: greater for cancer, diabetes, heart disease, HIV/AIDS, homicide; Hispanics vs. Whites: greater for diabetes
- *Morbidity* – For most ethnic minorities (Blacks, Native Americans, Hispanics and Asians) vs. Whites: higher for kidney failure; also for cancer, diabetes, hypertension, obesity, HIV/AIDS, tuberculosis, hepatitis
- Disparities persist even after accounting for socioeconomic status, insurance, lifestyle, and clinical factors
- Combined costs of health inequalities and premature death in the United States were $1.24 trillion[1]

1. LaVeist TA. Gaskin DJ. Richard P. THE ECONOMIC BURDEN OF HEALTH INEQUALITIES IN THE UNITED STATES. Joint Center for Political and Economic Studies September 2009

OPEN ACCESS Freely available online PLoS MEDICINE

Eight Americas: Investigating Mortality Disparities across Races, Counties, and Race-Counties in the United States

Christopher J. L. Murray[1,2,3], Sandeep C. Kulkarni[2,4], Catherine Michaud[2,3], Niels Tomijima[3], Maria T. Bulzacchelli[3], Terrell J. Iandiorio[3], Majid Ezzati[1,2*]

1 Harvard School of Public Health, Boston, Massachusetts, United States of America, 2 Harvard University Initiative for Global Health, Cambridge, Massachusetts, United States of America, 3 Center for Population and Development Studies, Harvard University, Cambridge, Massachusetts, United States of America, 4 University of California San Francisco, San Francisco, California, United States of America

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ABSTRACT

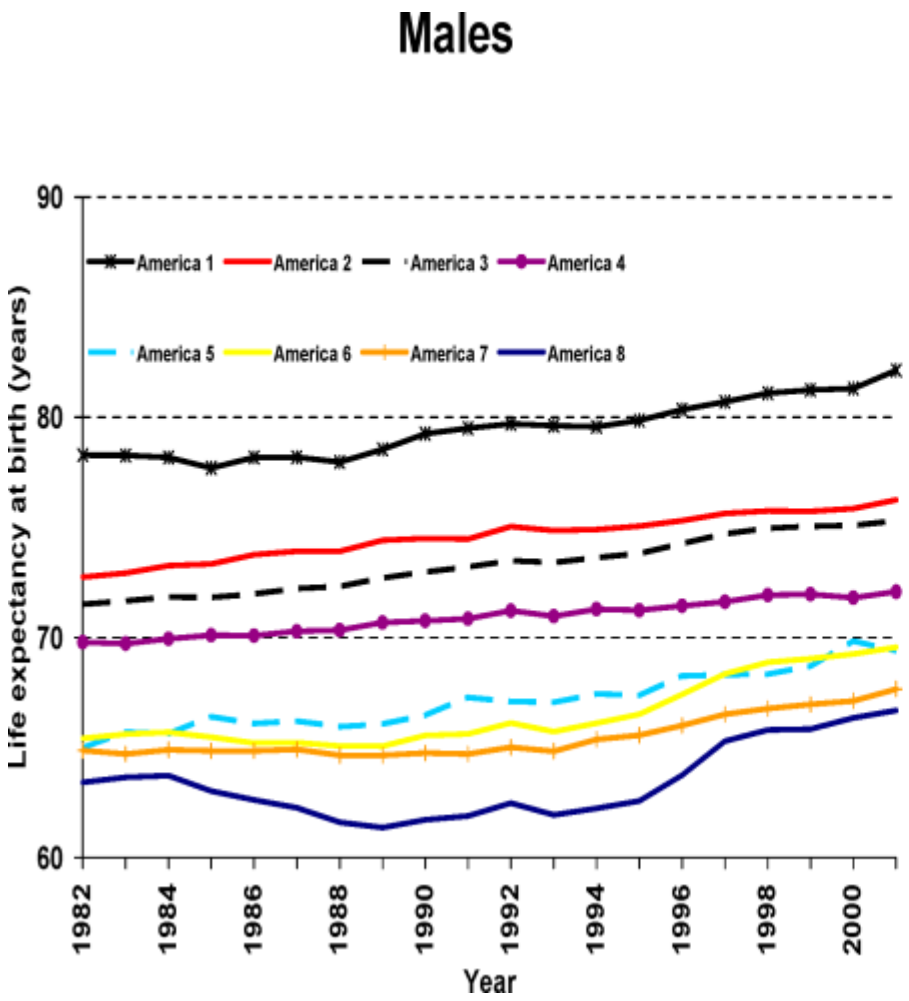
Background

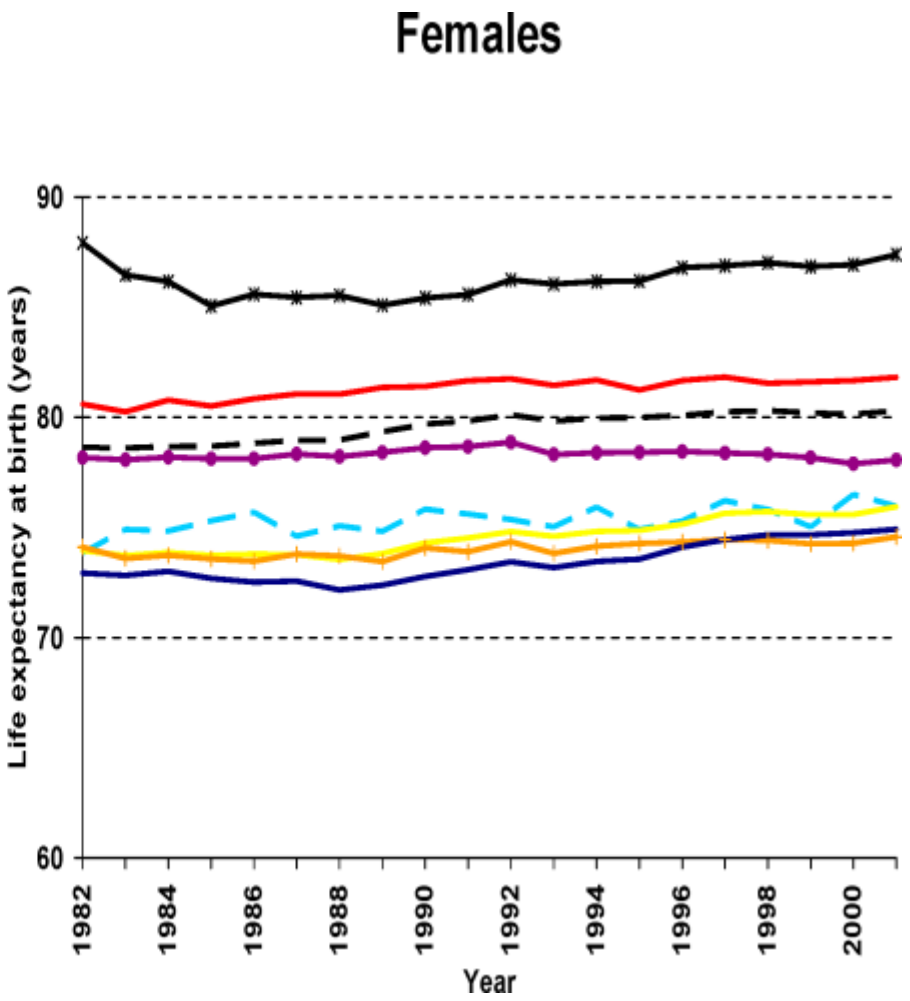
The gap between the highest and lowest life expectancies for race-county combinations in the United States is over 35 y. We divided the race-county combinations of the US population into eight distinct groups, referred to as the "eight Americas," to explore the causes of the disparities that can inform specific public health intervention policies and programs.

America	General Description	Population (Millions)	Average Income Per Capita	Percent Completing High School
1	Asian	10.4	$21,566	80%
2	Northland low-income rural white	3.6	$17,758	83%
3	Middle America	214.0	$24,640	84%
4	Low-income whites in Appalachia and the Mississippi Valley	16.6	$16,390	72%
5	Western Native American	1.0	$10,029	69%
6	Black Middle America	23.4	$15,412	75%
7	Southern low-income rural black	5.8	$10,463	61%
8	High-risk urban black	7.5	$14,800	72%

Murray CJ, Kulkarni SC, Michaud C, Tomijima N, Bulzacchelli MT, Iandiorio TJ, Ezzati M. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. PLoS Med. 2006 Sep;3(9):e260.

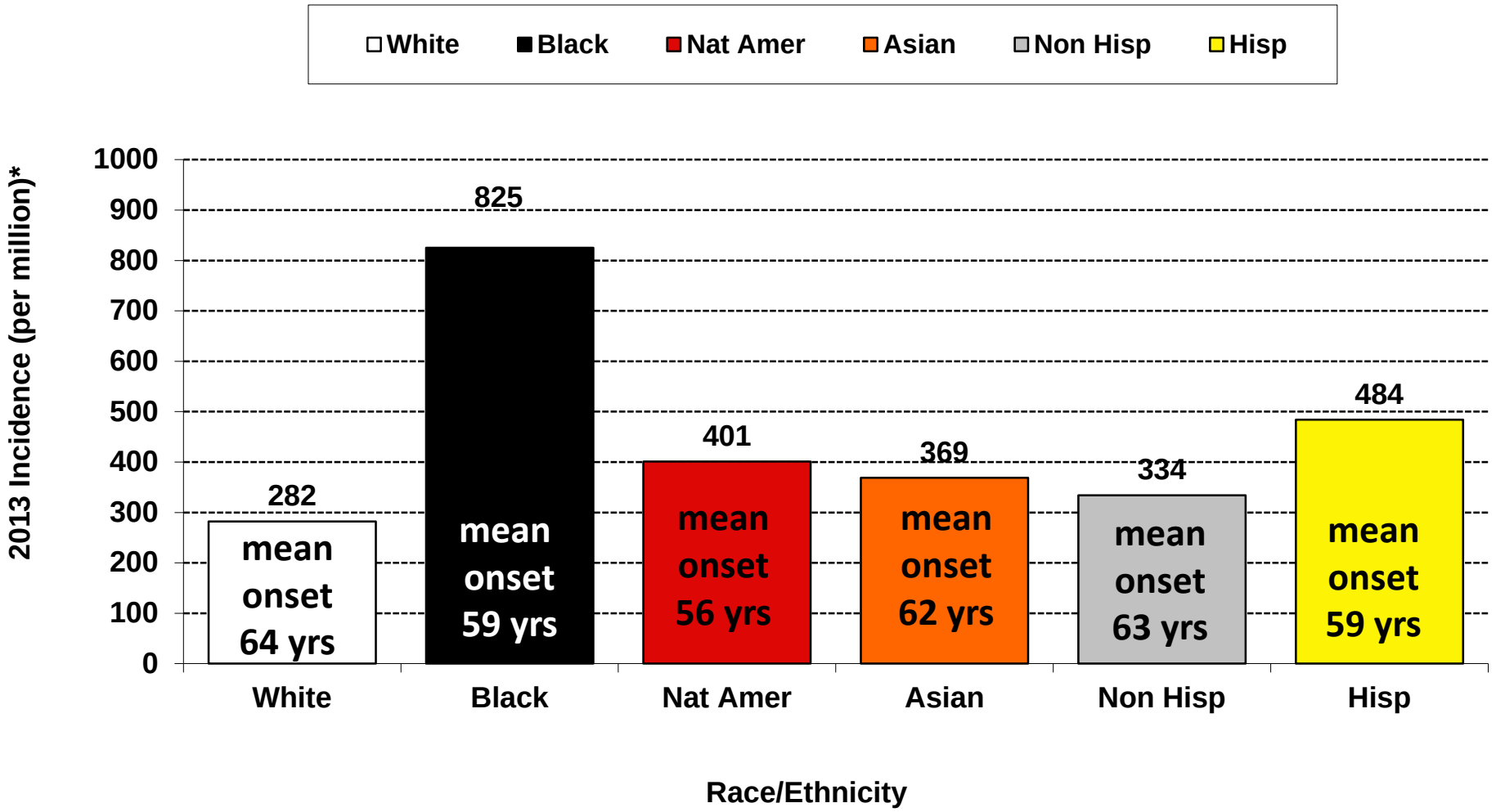
Mortality Experiences of the 8 Americas





Murray CJ, Kulkarni SC, Michaud C, Tomijima N, Bulzacchelli MT, Iandiorio TJ, Ezzati M. Eight Americas: investigating mortality disparities across races, counties, and race-counties in the United States. PLoS Med. 2006 Sep;3(9):e260.

Kidney Failure (End Stage Renal Disease) is up to 2.9 times greater in racial/ethnic minorities 2013



US Renal Data System Annual Data Report 2015; *adjusted for age, sex, race, ethnicity

Treating ESRD is costly, both personally and financially

	Age 50-54 expected remaining lifetime	Annual Medicare expenditures per person	Quality of Life
Dialysis patient	8 years	$85,000	↓
Transplant patient	20 years	$30,000	→
General population	30 years	$10,000	↑

→Need to pre-empt illness upstream through molecular knowledge, clinical therapeutics and behavioral interventions

CDC Home

Centers for Disease Control and Prevention

Your Online Source for Credible Health Information

Local Search

Chronic Kidney Disease (CKD) Surveillance Project

Tracking Kidney Disease in the United States

Website: nccd.cdc.gov/ckd/

Chronic Kidney Disease Home

FAQs | Glossary | Data Sources | Bibliography Contact us about CKD

CKD Topics

Complete Indicator List

Prevalence | Incidence | Awareness | Risk Factors | Health Consequences | Quality of Care | Health Care System Capacity

Select a Topic

Focus on Special Populations

- Children and Adolescents
- Solid Organ Transplant Population
- Native Americans
- Polycystic Kidney Disease Population

Focus on Risk Factors and Themes

- Age
- Diabetes
- Hypertension
- Race/Ethnicity
- Acute Kidney Injury (AKI)

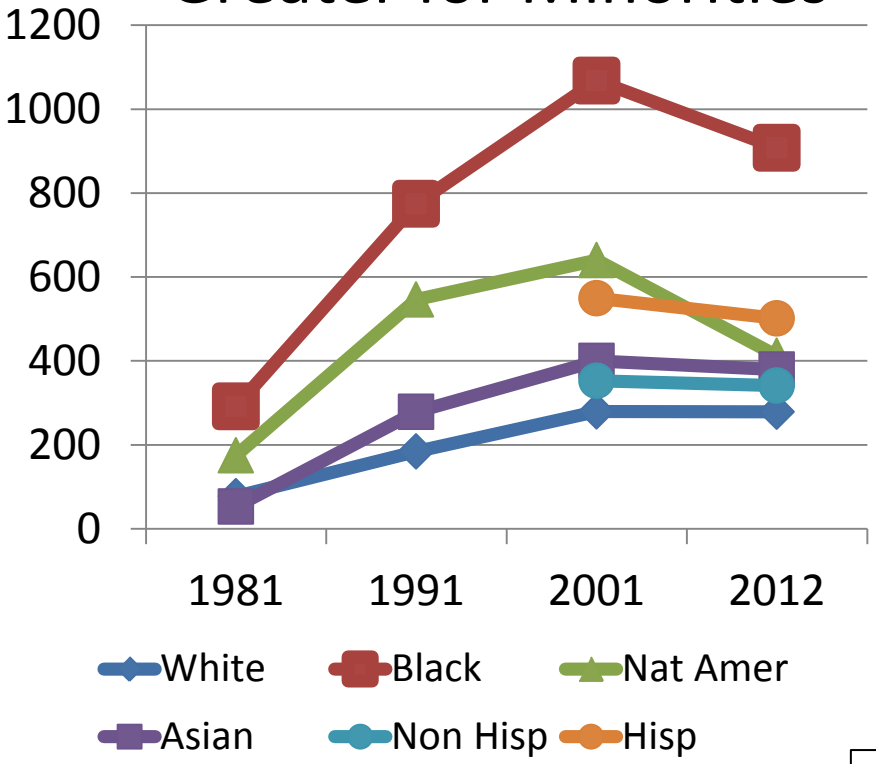
World Hypertension Day

Healthy People 2020

Healthy People 2020 provides national objectives for improving the health of all Americans. Fourteen (14) objectives focus on kidney disease, including end-

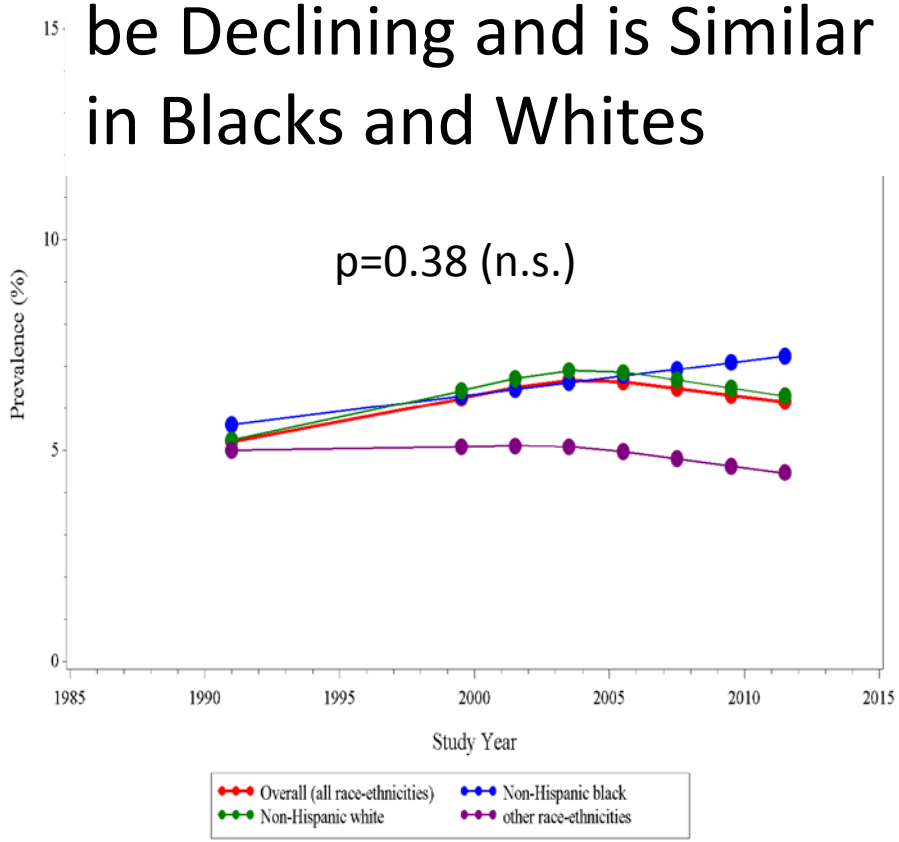
Over Three Decades

Incidence Rate of ESRD by Race May be Declining but Greater for Minorities



US Renal Data System Annual Data Report 2014; *adjusted for age and sex

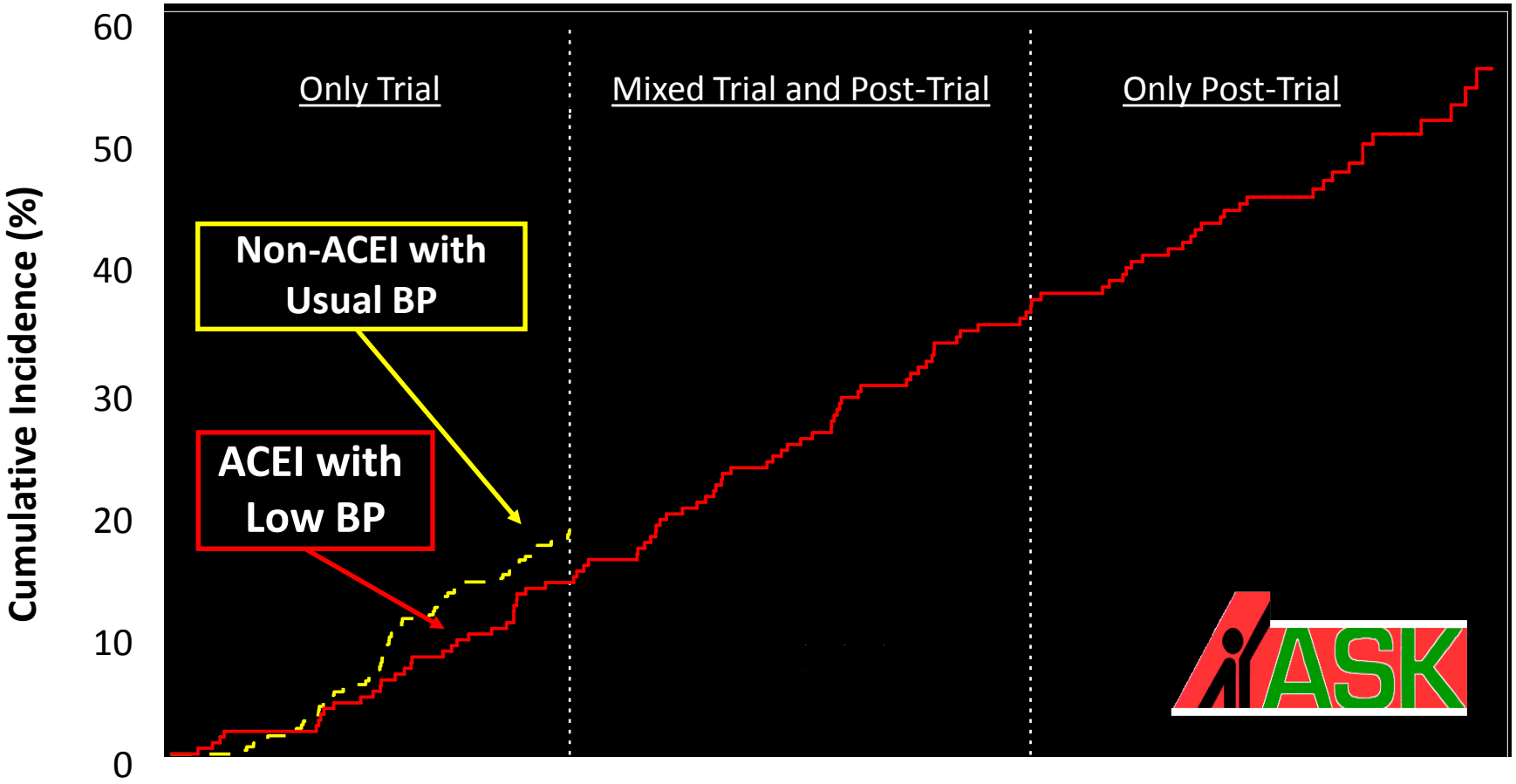
CKD Prevalence May Also be Declining and is Similar in Blacks and Whites



Murphy D, Charles E McCulloch CE, Lin F, Banerjee T, Bragg-Gresham JL Eberhardt MS, Morgenstern H, Pavkov ME, Saran R, Powe NR*, Hsu CY* Trends in prevalence of chronic kidney disease in the United States. 2015 ASN abstract (manuscript in preparation)

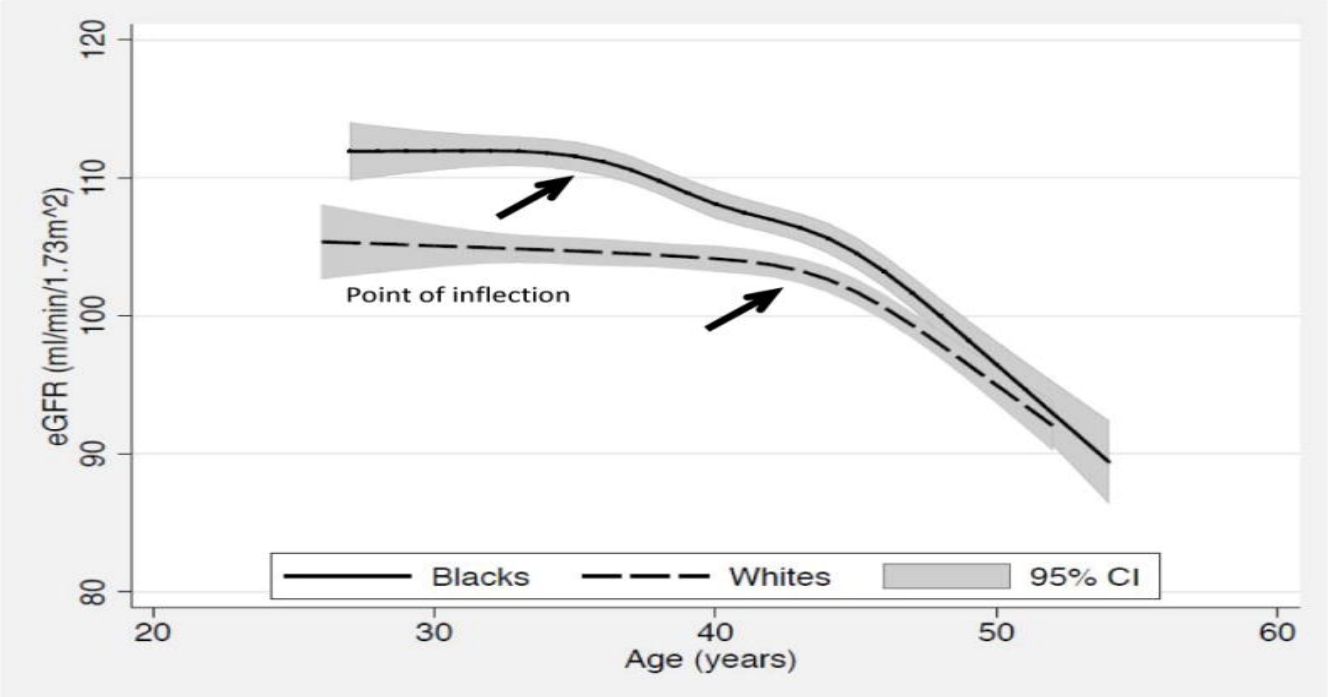
Relentlessness of CKD Progression in African Americans:

Cumulative Incidence of Events (Doubling of SCr, ESRD, or Death) in African American Study of Kidney Disease



Number At Risk										
Usual BP & non-ACEI:		324	293	273						
Low BP and ACEI:	215	210	196	183	168	151	130	120	104	63	23

Decline in $eGFR_{cys}$ Differs by Race at Early Ages, with Faster Annualized Rates of Decline Among Blacks



Age	P Value for Difference in Slope by Race
30	0.7
35	0.06
40	<0.001
45	0.09
50+	0.2

Peralta CA, Vittinghoff E, Bansal N, Jacobs D Jr, Muntner P, Kestenbaum B, Lewis C, Siscovick D, Kramer H, Shlipak M, Bibbins-Domingo K. Trajectories of kidney function decline in young black and white adults with preserved GFR: results from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Am J Kidney Dis. 2013 ;62(2):261-6.

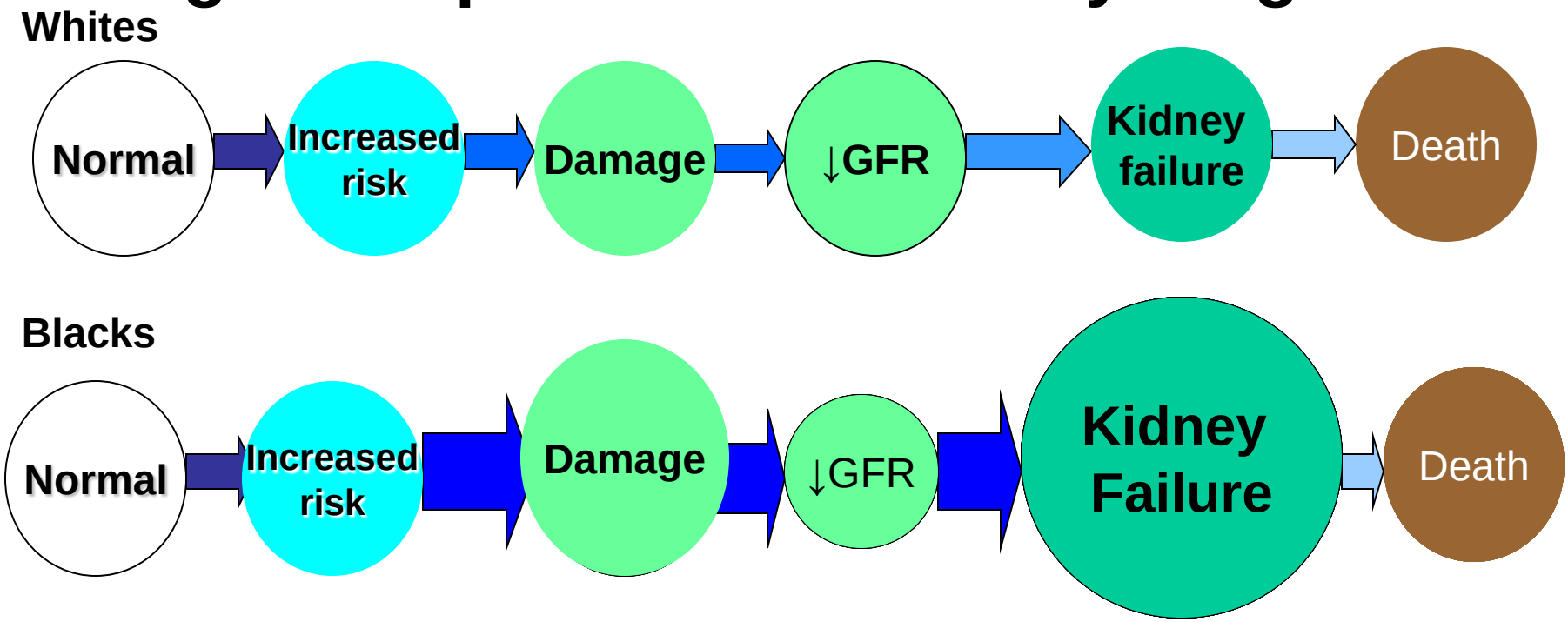
Risk of Projected* Kidney Failure Among 1,119,816 Adult in Kaiser Permanente Southern California is Greater for Blacks and Hispanics Compared to Whites

	Odds Ratios		
Time after Entry eGFR	**Black vs White**	**Hispanic vs White**	**Asian vs White**
1 y	2.17 (1.89–2.49)	1.78 (1.56–2.02)	1.47 (1.20–1.80)
3 y	1.53 (1.45–1.61)	1.30 (1.24–1.36)	1.10 (1.03–1.19)
5 y	1.34 (1.29–1.39)	1.15 (1.12–1.19)	0.99 (0.94–1.04)
During Study Period			
Any entry eGFR	1.34 (1.30–1.38)	1.08 (1.05–1.10)	0.89 (0.85–0.92)
Entry eGFR ≥60 mL/min/1.73 m^2	1.19 (1.47–1.23)	0.92 (0.89–0.94)	0.69 (0.66–0.73)
Entry eGFR <60 mL/min/1.73 m^2	1.54 (1.46–1.62)	1.49 (1.42–1.56)	1.41 (1.32–1.51)

*Projected based on >2 serum creatinine tests and >180 days between tests from 2003–2009 : 526,498 whites, 350,919 Hispanics, 136,923 blacks, and 105,476 Asians.

Derose SF, Rutkowski MP, Crooks PW, Shi JM, Wang JQ, Kalantar-Zadeh K, Kovesdy CP, Levin NW, Jacobsen SJ. Racial differences in estimated GFR decline, ESRD, and mortality in an integrated health system. Am J Kidney Dis. 2013 Aug;62(2):236-44.

The higher incidence of kidney failure among African Americans appears due to a faster rate of disease progression rather than greater prevalence of early stage CKD



What are the contributing factors to this acceleration?

Susceptibility, initiation and progression factors contributing to excess ESRD incidence

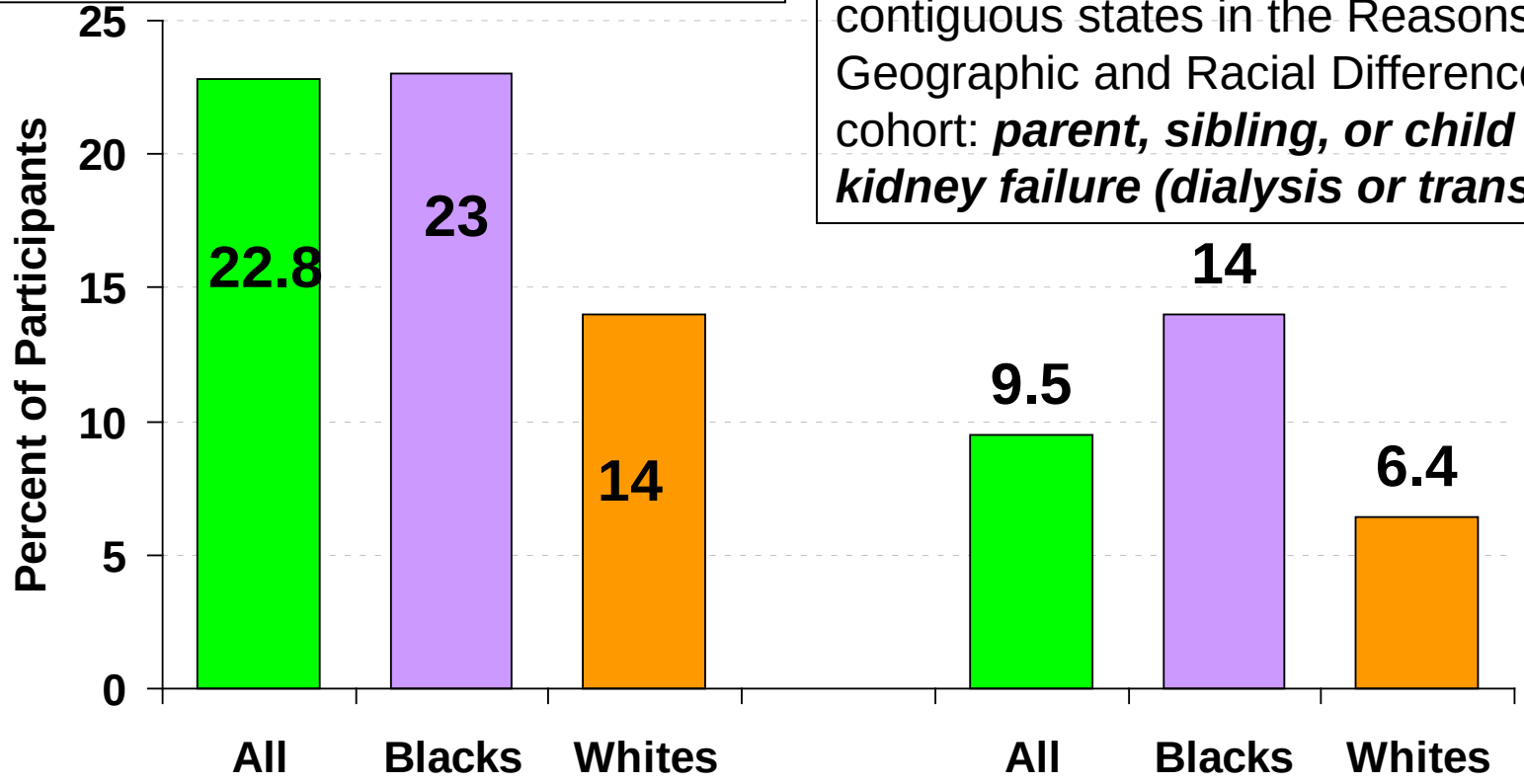
- Biological
- Environmental
- Behavioral (e.g. lifestyle)
- Quality/adequacy of CKD care

Blacks are more likely to have a family history of ESRD than Whites

Of 25,883 patients starting dialysis in southeast U.S : ***1st or 2nd degree relative who was also being treated for ESRD***

REGARDS
REasons for Geographic And Racial Differences in Stroke

12,030 US residents 45 yr and older in NC, SC, GA, TN, MS AL, LA, AR and contiguous states in the Reasons for Geographic and Racial Differences in cohort: ***parent, sibling, or child with kidney failure (dialysis or transplant)***



•Freedman BI, Volkova NV, Satko SG, Krisher J, Jurkovitz C, Soucie JM, McClellan WM. Population-based screening for family history of end-stage renal disease among incident dialysis patients. *Am J Nephrol*. 2005 ;25(6):529-35.

•McClellan W, Speckman R, McClure L, Howard V, Campbell RC, Cushman M, Audhya P, Howard G, Warnock DG. Prevalence and Characteristics of a Family History of ESRD among Adults in the US Population. *J Am Soc Nephrol*. 2007 Apr;18(4):1344-52.

Overview of the Choices for Healthy Outcomes in Caring for ESRD Study

CHOICE
CHOICE
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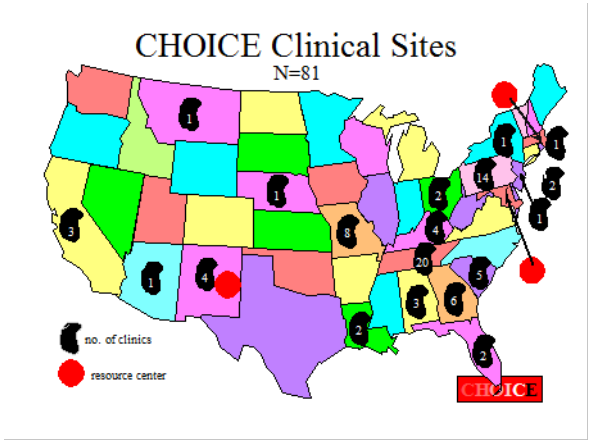
CHOICE

- **Design**: National prospective cohort study comparing effectiveness of hemodialysis and peritoneal dialysis
- **Population**:1041 new-onset adult ESRD patients in 81 clinics in US enrolled Oct 1995-Jun 1998 providing informed consent



- **Follow-up**: range 6 months to 9 years
- **Support:** since 1994 by 2 NIDDK, 1 NHLBI, 1 AHRQ grant
- **Current RO1:** Retained Organic Solutes and Clinical Outcomes in Hemodialysis
- **K awards and fellow research** - Coresh, Longenecker, Boulware, Astor, Miskulin, Shafer, Unruh, Melamed, Cavanaugh, Crews, Shafi, Scialla

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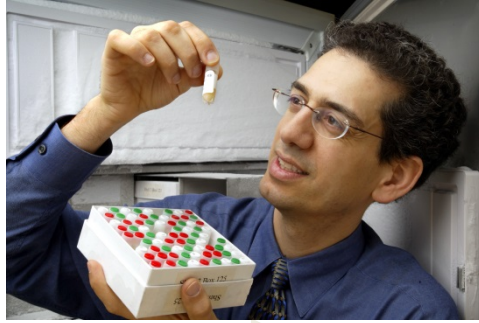
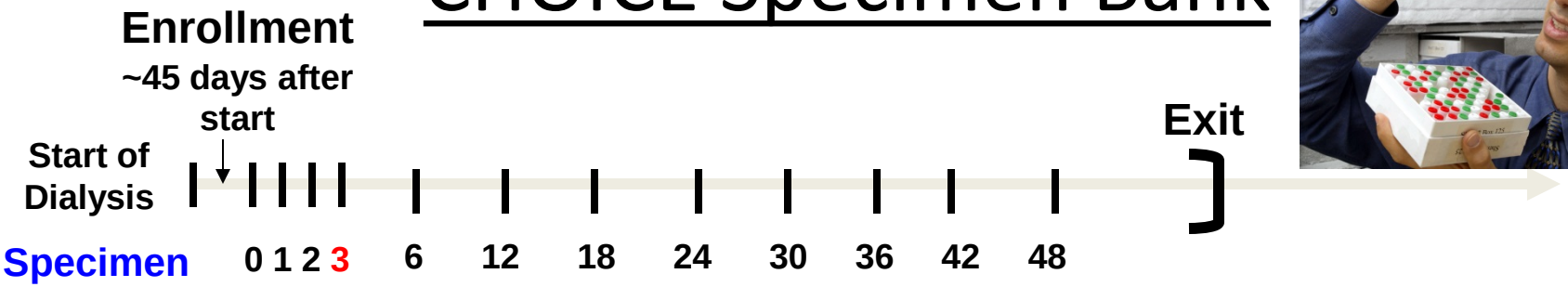
CHOICE Specimen Bank





1041 enrolled

	N	n-Visits	n-Vials
•Total	895	13,502 (8 routine + 1 special)	91,231
	Measurements		~10,000
•Serum	Lp(a) levels + isoforms, CRP, IL-6, MMP3, p-selectin, TNF-beta		
•Plasma	Fibrinogen, PTH, iPTH		
•DNA	16 candidates genes		
	Illumina panel - 1536 SNPs; 164 CVD genes; 87 admixture markers		
	646 genomic DNA + 179 WGA DNA + QC of WGA		

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Issues Addressed in the CHOICE Study

CHOICE
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- **Risk Factors & Prevention**
  - Risk factors for CVD
- **Diagnosis**
  - Detection of Comorbid Disease
- **Etiology**
  - **Genetics**
  - Small organic solutes and outcomes in dialysis
  - Inflammation
- **Therapy**
  - Hemodialysis vs Peritoneal dialysis
    - Mortality, quality of life, patient satisfaction
  - Dose of dialysis
  - Statin use and sepsis
- **Prognosis**
  - Residual renal function and survival
  - Comorbidity and survival
  - Cholesterol & mortality
  - Phosphate & mortality
- **CKD Complications**
  - Anemia
  - Bone and mineral disease
  - Blood pressure, PAD
  - Sudden cardiac death
- **Access (Equity) to Care**
  - Referral to nephrologist
- **Quality & Safety of Care**
  - Multidisciplinary rounds
  - Clinical practice guidelines
  - Vascular access monitoring
  - Peritoneal dialysis experience and outcomes
- **Resource Use/Costs**
  - Patient-physician contact

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83 study publications, 4 RO1s, multiple K awards and trainee projects

nature genetics

Case-control design in Choices for Healthy Outcomes in Caring for ESRD (CHOICE) Study participants

MYH9 is associated with nondiabetic end-stage renal disease in African Americans

W H Linda Kao[1–3,25], Michael J Klag[1–3,25], Lucy A Meoni[2–4], David Reich[5,6], Yvette Berthier-Schaad[1], Man Li[1], Josef Coresh[1–4], Nick Patterson[6], Arti Tandon[5,6], Neil R Powe[1–3], Nancy E Fink[1–3], John H Sadler[7], Matthew R Weir[7], Hanna E Abboud[8], Sharon G Adler[9], Jasmin Divers[10], Sudha K Iyengar[11], Barry I Freedman[10], Paul L Kimmel[12], William C Knowler[13], Orly F Kohn[14], Kristopher Kramp[11], David J Leehey[15], Susanne B Nicholas[16], Madeleine V Pahl[17], Jeffrey R Schelling[18], John R Sedor[18,19], Denyse Thornley-Brown[20], Cheryl A Winkler[21], Michael W Smith[21,24] & Rulan S Parekh[1–3,22], on behalf of the Family Investigation of Nephropathy and Diabetes (FIND) Research Group[23]

Nat Genet. 2008 Oct;40(10):1185-92.

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Summary of studies of *MYH9* or *APOL1* genetic variants

Table 1 | Summary of studies of *MYH9* or *APOL1* genetic variants

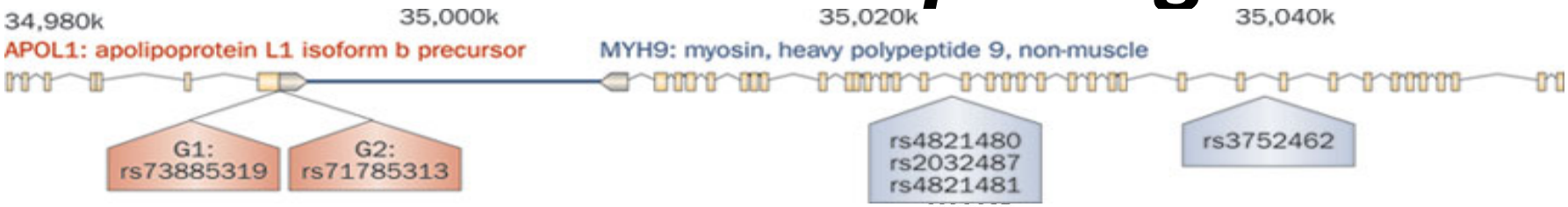
Population and etiology	Variant	OR	*P* value	Patients (cases/controls)	Reference
African American					
Nondiabetic ESRD (not biopsy-proven)	*MYH9* E1	2.2	1.72×10^{-11}	669/806	Kao *et al.* (2008)[22]
	MYH9 E1	2.5	8.48×10^{-17}	871/948	Freedman *et al.* (2009)[91]
	MYH9 E1	2.0	2.57×10^{-03}	346/140	Behar *et al.* (2010)[96]
	APOL1 G1	4.9	3.50×10^{-04}	346/140	Tzur *et al.* (2010)[35]
Biopsy-proven FSGS	*MYH9* E1	4.5	1.00×10^{-13}	188/370	Kopp *et al.* (2008)[23]
	MYH9 E1	3.7	3.98×10^{-06}	87/806	Kao *et al.* (2008)[22]
	APOL1 G1 or G2	10.5	1.07×10^{-23} (G1)*; 4.38×10^{-07} (G2)*	192/176	Genovese *et al.* (2010)[36]
Biopsy-proven HIVAN	*MYH9* E1	5.3	2.00×10^{-06}	53/241	Kopp *et al.* (2008)[23]
Biopsy-proven HIVAN and FSGS	*MYH9* E1	4.9	2.20×10^{-20}	241/611	Nelson *et al.* (2010)[95]
Hypertensive ESRD (not biopsy-proven)	*MYH9* E1	1.9	2.00×10^{-03}	288/192	Kopp *et al.* (2008)[23]
	MYH9 E1	2.1	3.70×10^{-07}	347/806	Kao *et al.* (2008)[22]
	MYH9 E1	2.6	3.20×10^{-11}	696/948	Nelson *et al.* (2010)[95]
	MYH9 E1	2.4	8.66×10^{-14}	696/948	Freedman *et al.* (2009)[91]
	APOL1 G1 or G2	7.3	1.00×10^{-63}*	1,002/923	Genovese *et al.* (2010)[36]
T2DM and ESRD (not biopsy-proven)	*MYH9* E1	NS	NS	284/192	Kopp *et al.* (2008)[23]
	MYH9 E1	1.3	5.6×10^{-03}	751/925	Freedman *et al.* (2009)[94]
Hispanic American					
Diabetes-unrelated ESRD (not biopsy-proven)	*MYH9* E1	3.7	6.88×10^{-03}	89/308	Behar *et al.* (2010)[96]
	APOL1 G1	15.5	8.80×10^{-04}	89/308	Tzur *et al.* (2010)[35]
European American					
Biopsy-proven FSGS	*MYH9* E1	9.7	2.00×10^{-02}	221/125	Kopp *et al.* (2008)[23]
American Indian					
Kidney dysfunction (not biopsy-proven)	*MYH9* SNPs	NS	NS	1,119	Franceschini *et al.* (2010)[93]

For consistency, all ORs and *P* values presented for *MYH9* are for the SNP E1 rs4821480, after global ancestry adjustments, when available. The risk for the variants shown is for a recessive mode of inheritance, except the *P* values for Genovese *et al.* (2010)[36], marked by *, which are of an allelic test. Some cohorts have been used more than once in these studies. Abbreviations: ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HIVAN, HIV-associated nephropathy; NS, not significant; OR, odds ratio; SNP, single nucleotide polymorphism.

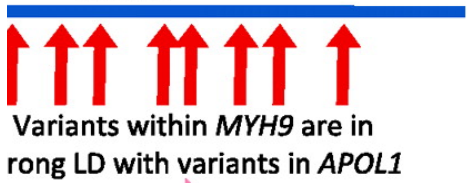
Rosset, S. *et al.* (2011) The population genetics of chronic kidney disease: insights from the *MYH9–APOL1* locus *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2011.52

nature REVIEWS NEPHROLOGY

Structure of the *ApoL1* gene

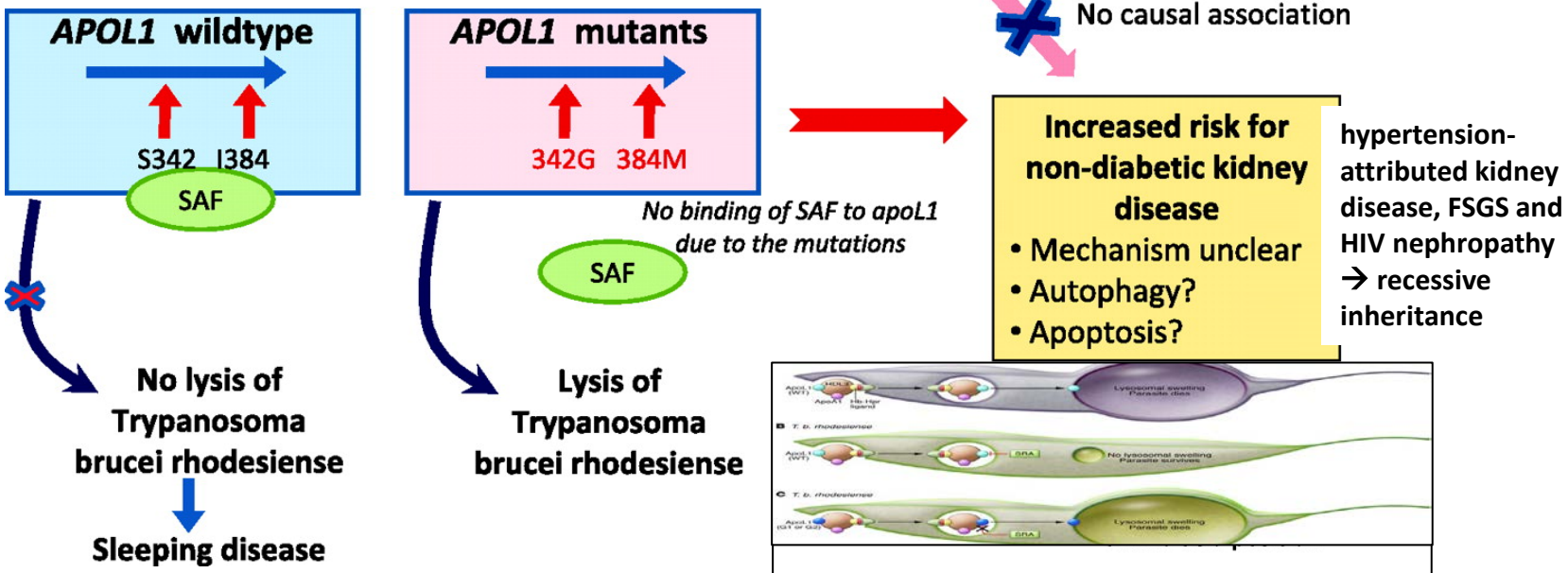


- 14.5 kb gene on chromosome 22
- Located 14 kb downstream of *MYH9*
- Encodes 398 amino acids



Variants within *MYH9* are in rong LD with variants in *APOL1*

No causal association

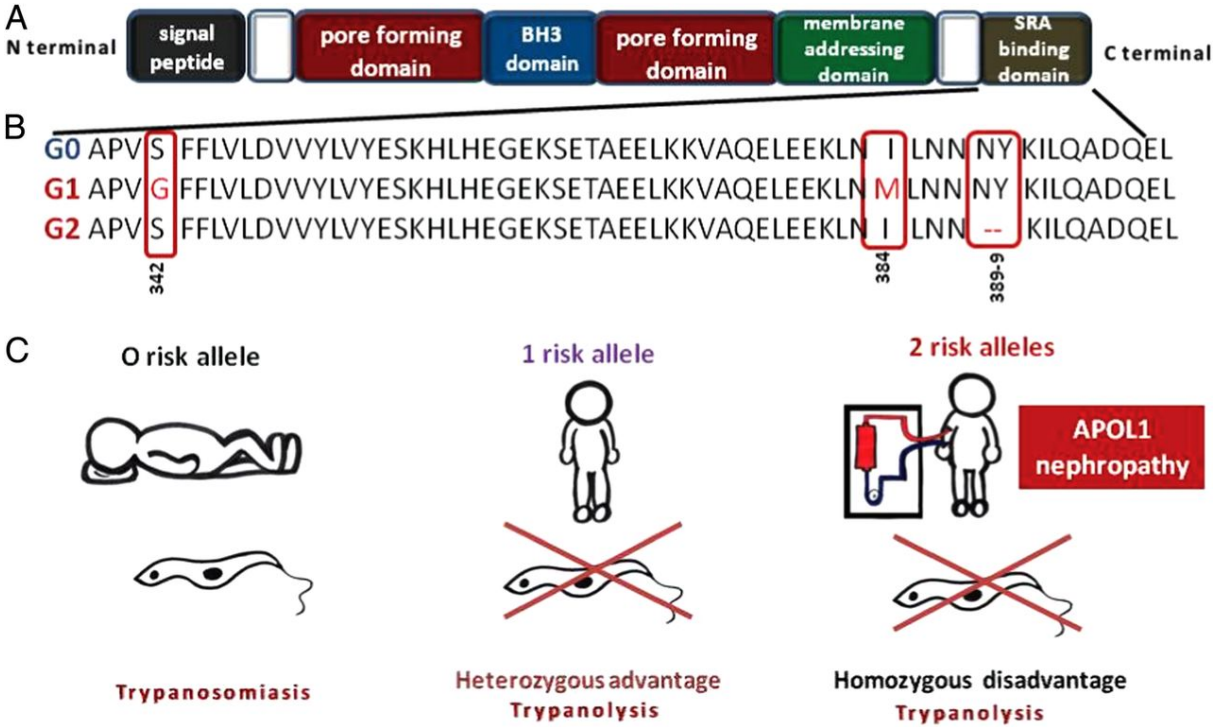


Madhavan, Sethu M. O'Toole JF . "The biology of APOL1 with insights into the association between APOL1 variants and chronic kidney disease." *Clinical and experimental nephrology* 18.2 (2014): 238-242.

Drawz, Paul E., and John R. Sedor. "The genetics of common kidney disease:." *Nature Reviews Nephrology* 7.8 (2011): 458-468.

Kruzel-Davila E, Wasser WG, Aviram S, Skorecki K APOL1 nephropathy: from gene to mechanisms of kidney injury Nephrol Dial Transplant (2015) 0: 1–10

Structure of ApoL1 (with annotated domains)

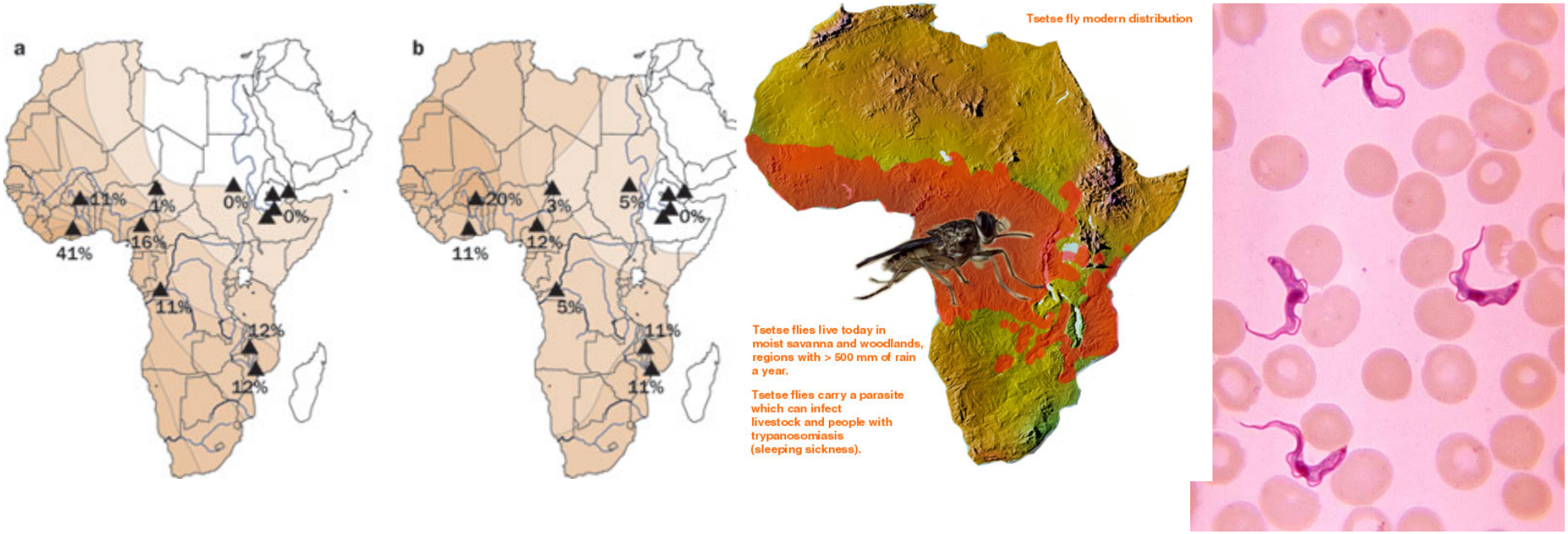


- 43 kDa protein - apolipoprotein family
- Produces a secreted protein bound to circulating HDL particles
- Expressed in various organs including kidney (podocytes, renal tubule cells, and glomerular endothelial cells)
- Involved in the autophagy pathway

NDT
Nephrology Dialysis Transplantation

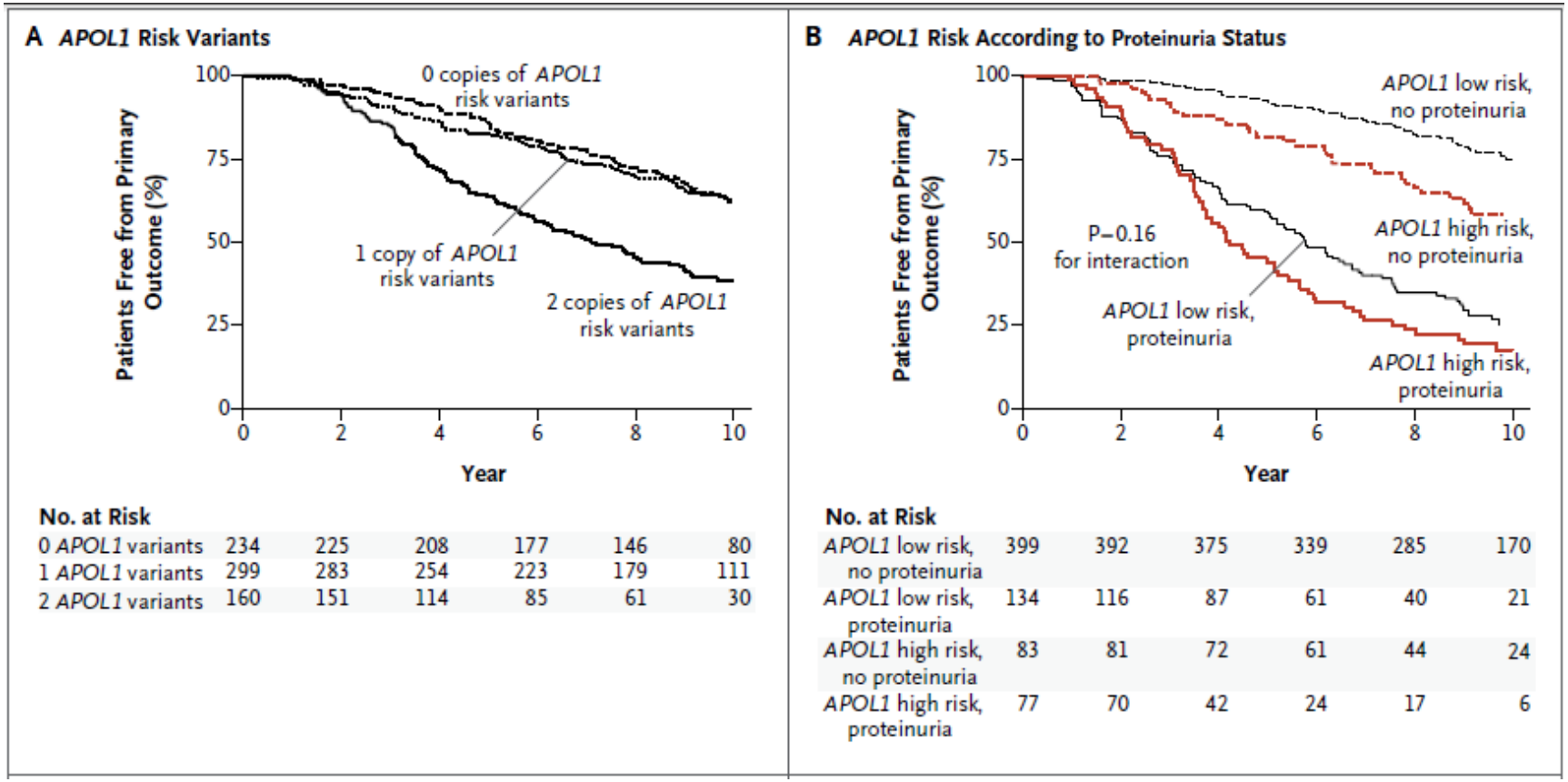
Etty Kruzel-Davila et al. Nephrol. Dial. Transplant. 2015;ndt.gfu391

Contour maps of allele frequency distributions of identified *APOL1* risk variants



nature REVIEWS NEPHROLOGY

AASK: APOL1 and CKD Progression in Longitudinal Studies

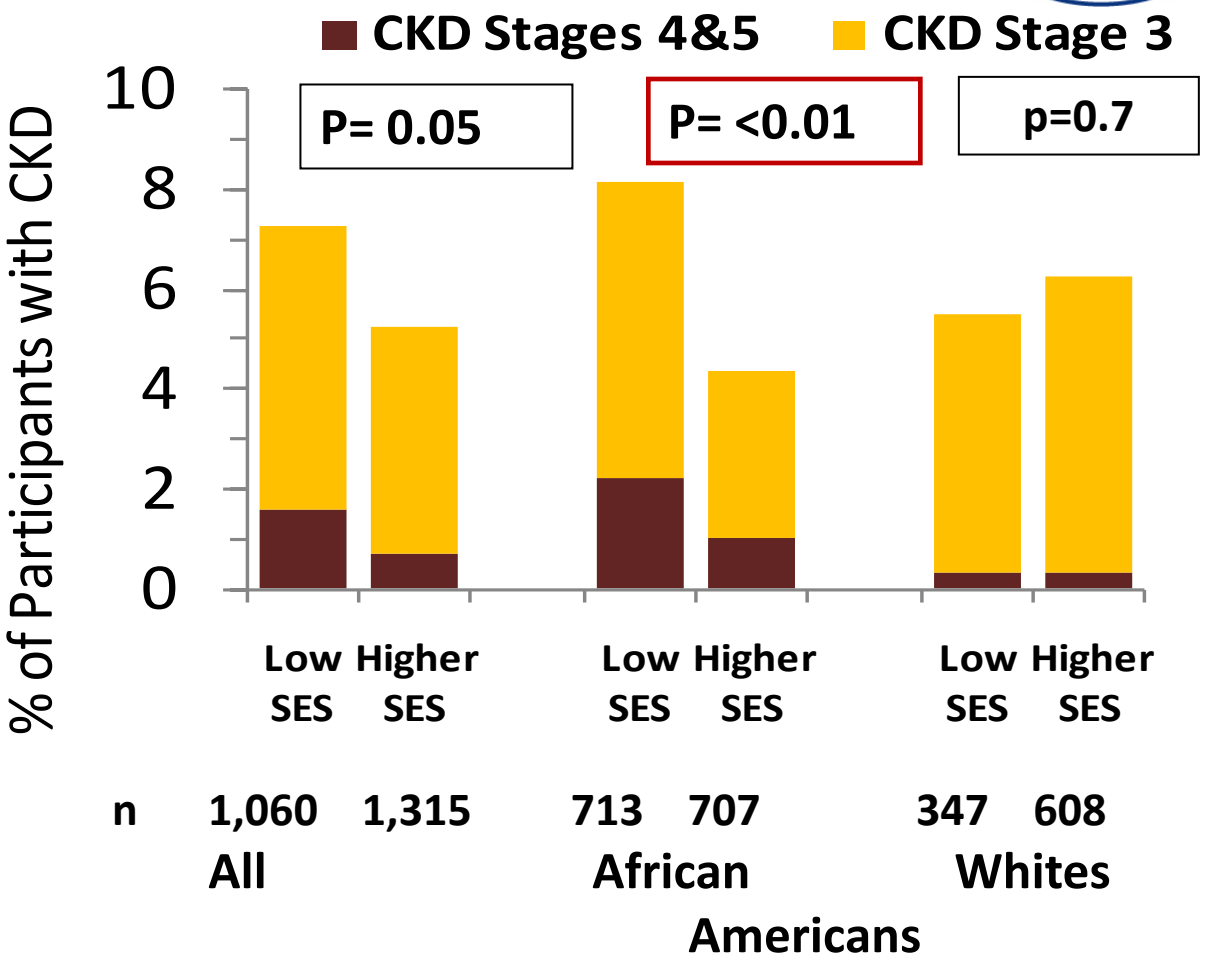


Parsa A, Kao WH, Xie D, Astor BC, Li M, Hsu CY, Feldman HI, Parekh RS, Kusek JW, Greene TH, Fink JC, Anderson AH, Choi MJ, Wright JT Jr, Lash JP, Freedman BI, Ojo A, Winkler CA, Raj DS, Kopp JB, He J, Jensvold NG, Tao K, Lipkowitz MS, Appel LJ; AASK Study Investigators; CRIC Study Investigators. APOL1 risk variants, race, and progression of chronic kidney disease. N Engl J Med. 2013 5;369(23):2183-96.

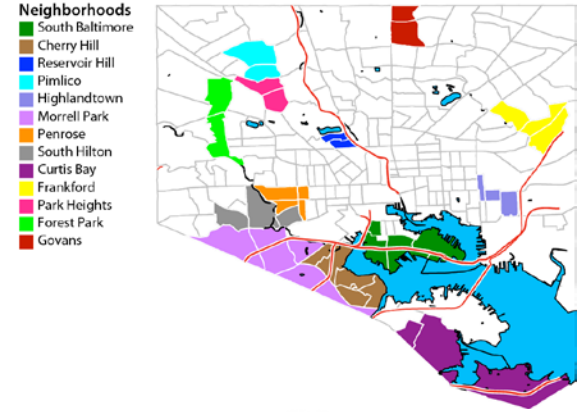
Factors contributing to Excess ESRD Incidence

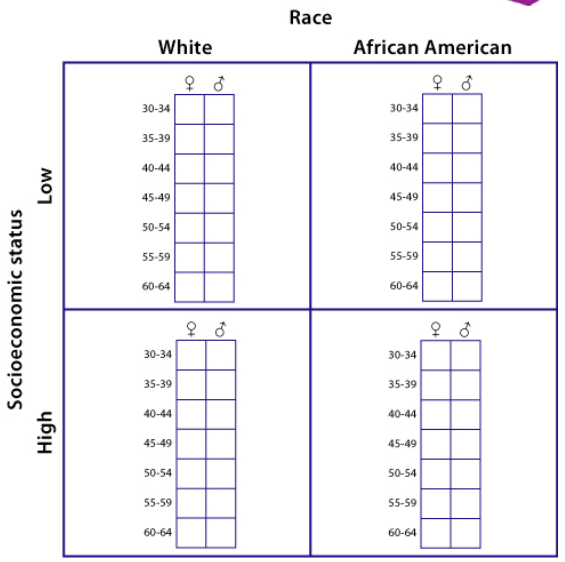
- Biological
- **Environmental**
- Behavioral (e.g. lifestyle)
- Quality/adequacy of CKD care

Association of Poverty with CKD (eGFR <60) is Modified by Race



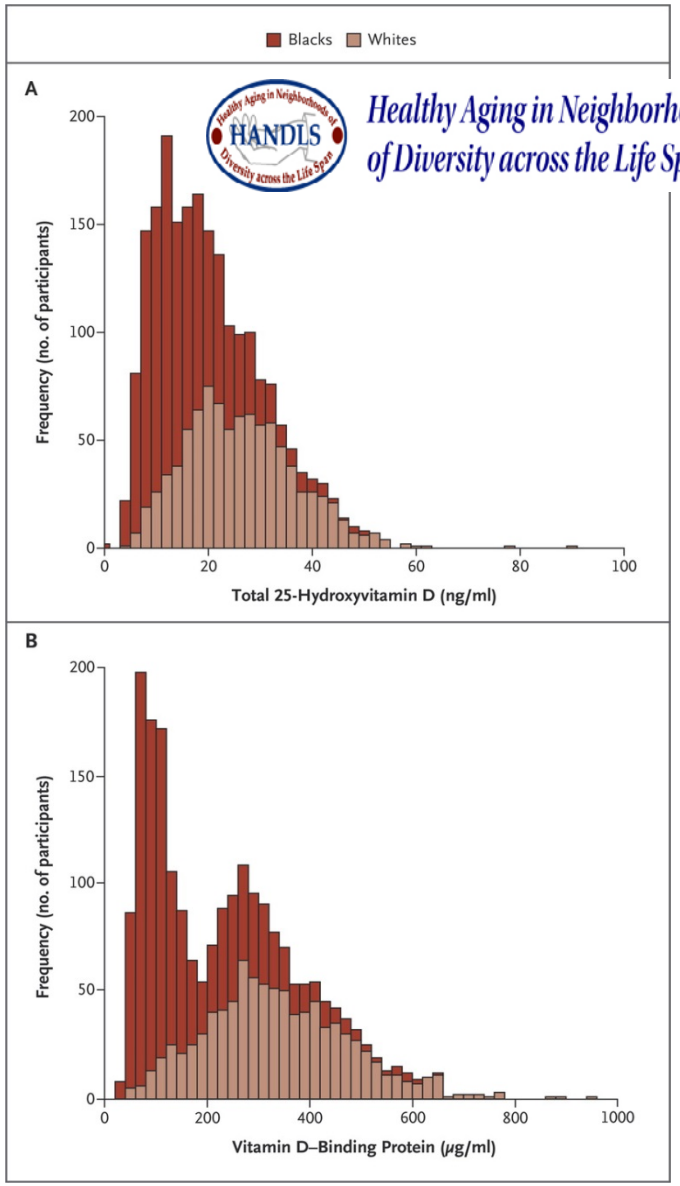
Healthy Aging in Neighborhoods of Diversity across the Life Span



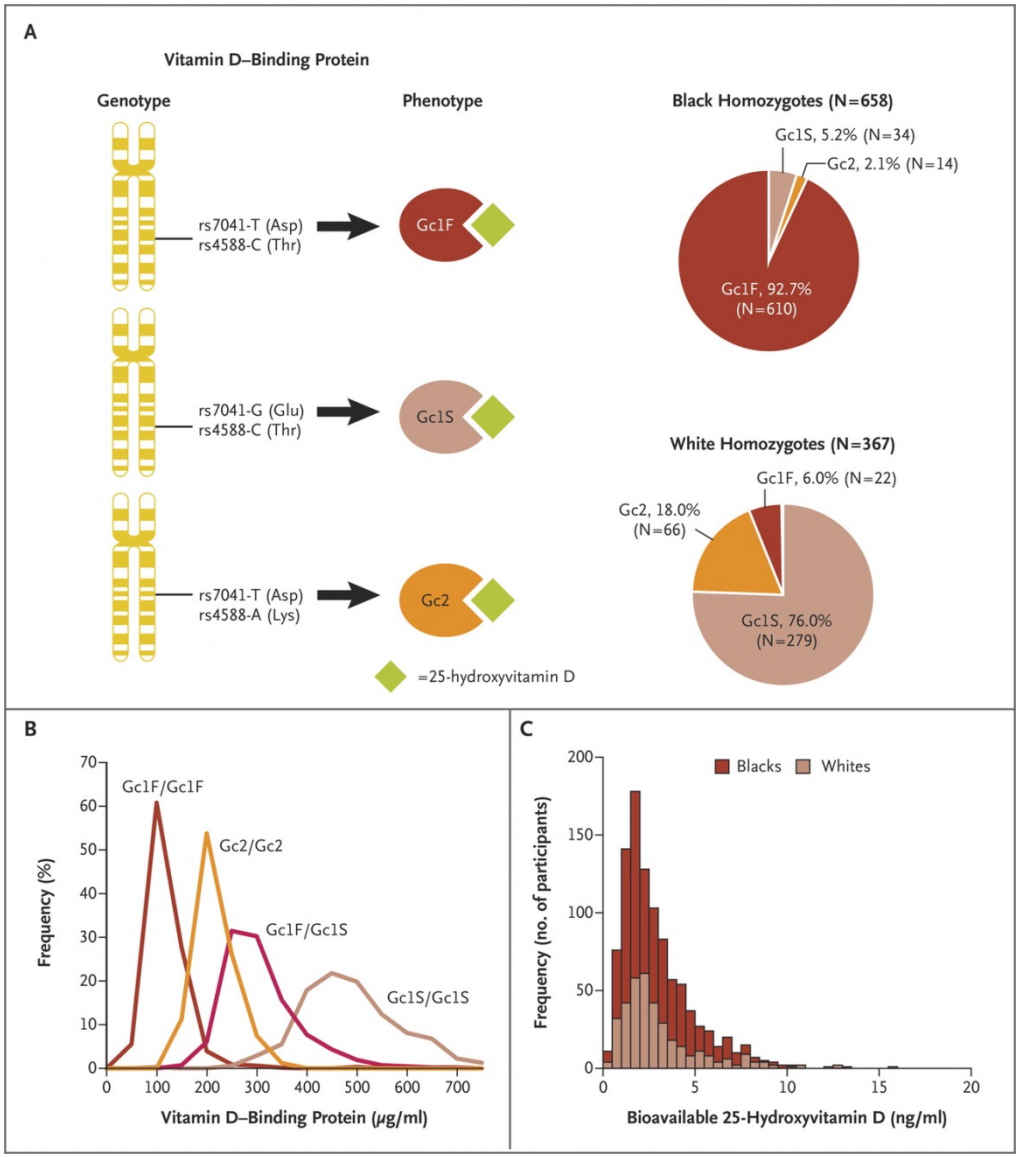


Crews DC, Charles RF, Evans MK, Zonderman AB, Powe NR. Poverty, Race and CKD in a Racially and Socioeconomically diverse urban population. Am J Kidney Dis. 2010 Mar 5.

Total 25-Hydroxyvitamin D and Vitamin D–Binding Protein Levels in Community-Dwelling White and Black Participants



Variant Vitamin D–Binding Proteins and Bioavailable 25-Hydroxyvitamin D



Powe CE et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013;369:1991-2000.

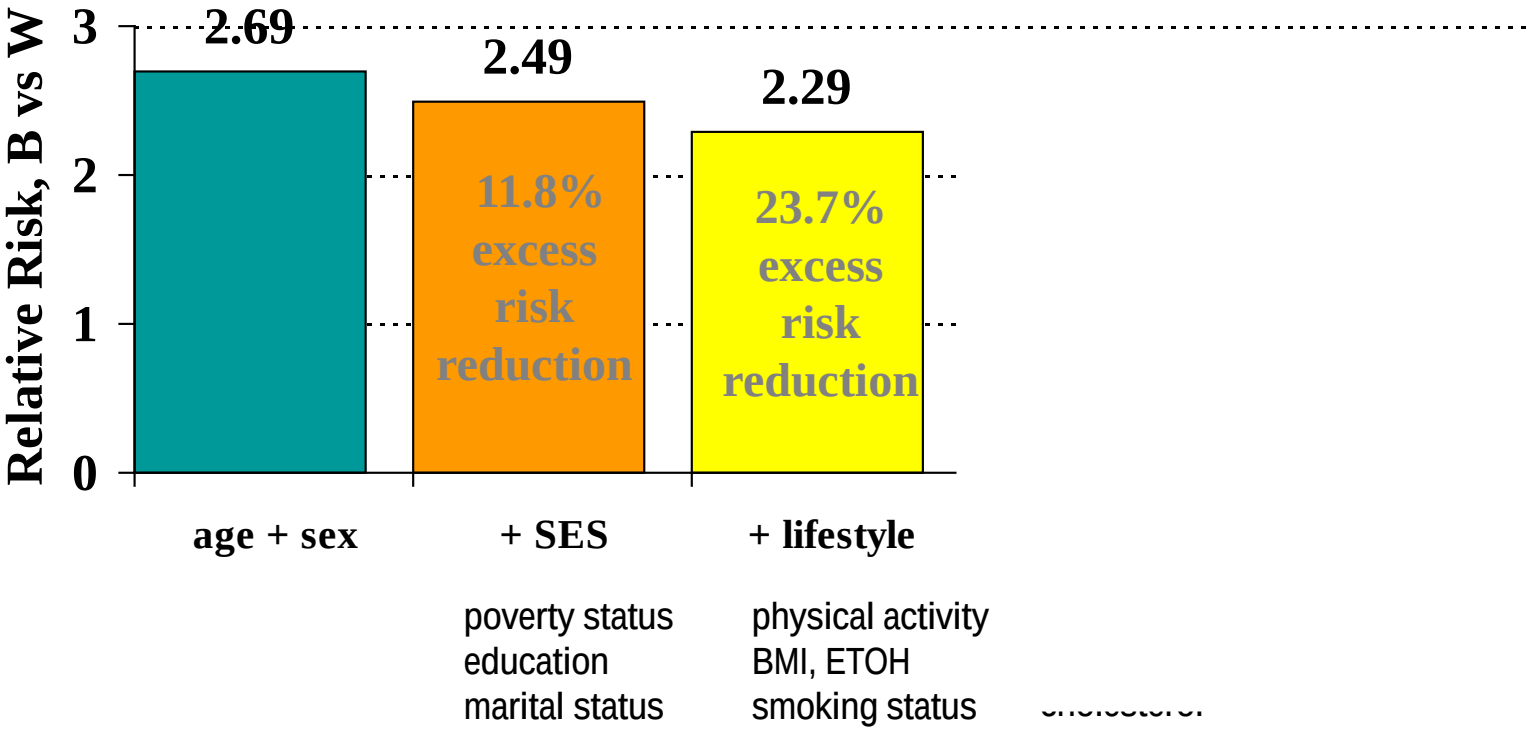
The NEW ENGLAND JOURNAL of MEDICINE

Factors contributing to Excess ESRD Incidence

- Biological
- Environmental
- Behavioral (e.g. lifestyle)
- Quality/adequacy of CKD care

Socioeconomic Status and Lifestyle Factors Explains 44% of the 3-fold excess risk of CKD in African Americans vs Whites

NHANES II (nationally representative)



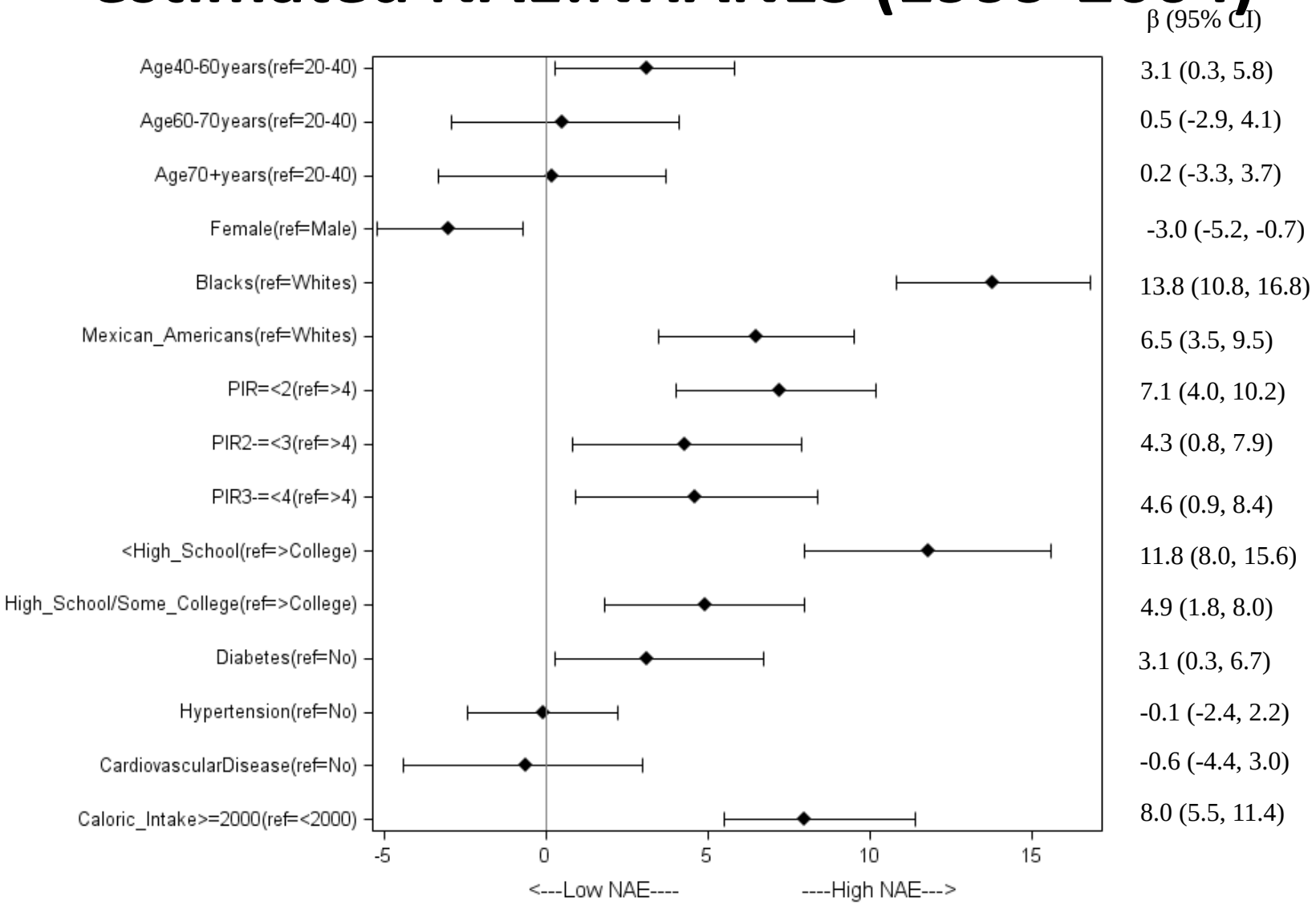
Tarver-Carr M, Powe NR, Eberhardt M, LaVeist TA, Kington RS, Coresh J, Brancati F. Excess Risk of Chronic Kidney Disease among African-American versus White Subjects in the United States: A Population-Based Study of Potential Explanatory Factors.*Journal American Society Nephrology*. 2002;13:2363-70.

High Dietary Acid Load and Progression to End Stage Renal Disease

- Study Design: National cohort study of 1486 adults with CKD enrolled in the NHANES III
- Exposure: Dietary acid load determined by 24-hour dietary recall questionnaire
- Outcome: ESRD over a median 14.2 years of follow-up through linkage with the Medicare ESRD Registry
- Confounders: demographics, nutritional factors, clinical factors, and kidney function/damage markers and accounting for intervening mortality events

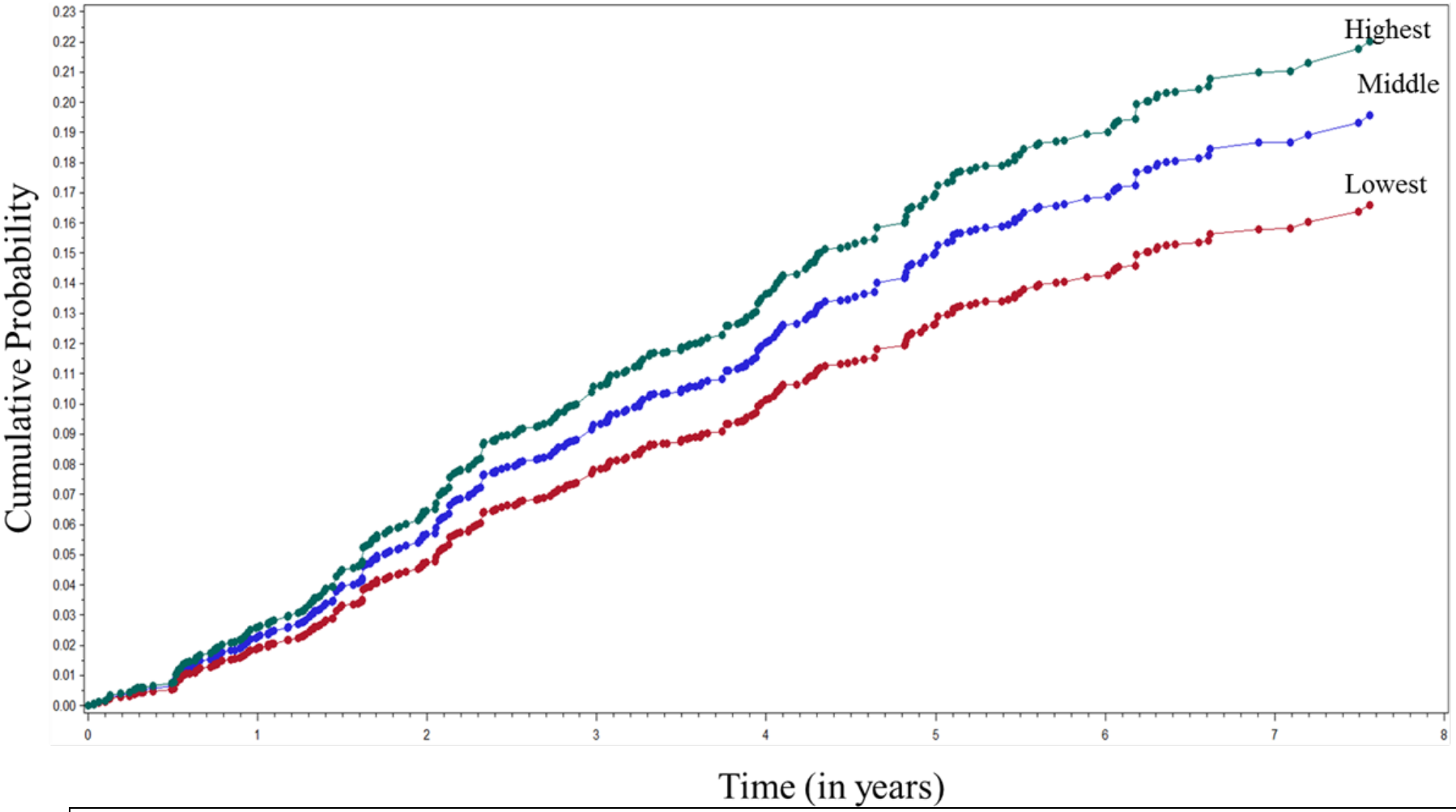
Banerjee T, Crews DC, Wesson DE, Tilea A, Saran R, Rios Burrows N, Williams DE, Powe NR; High Dietary Acid Load Predicts ESRD among Adults with CKD. *Journal of the American Society of Nephrology* 2015 : 26(7):1693-700

Association of Participant Characteristics with estimated NAE:NHANES (1999-2004)



Adjusted β coefficients, from median regression. Points show β coefficients per quintile, and bars show 95% confidence intervals.

Cumulative probability of ESRD with varying levels of dietary acid load

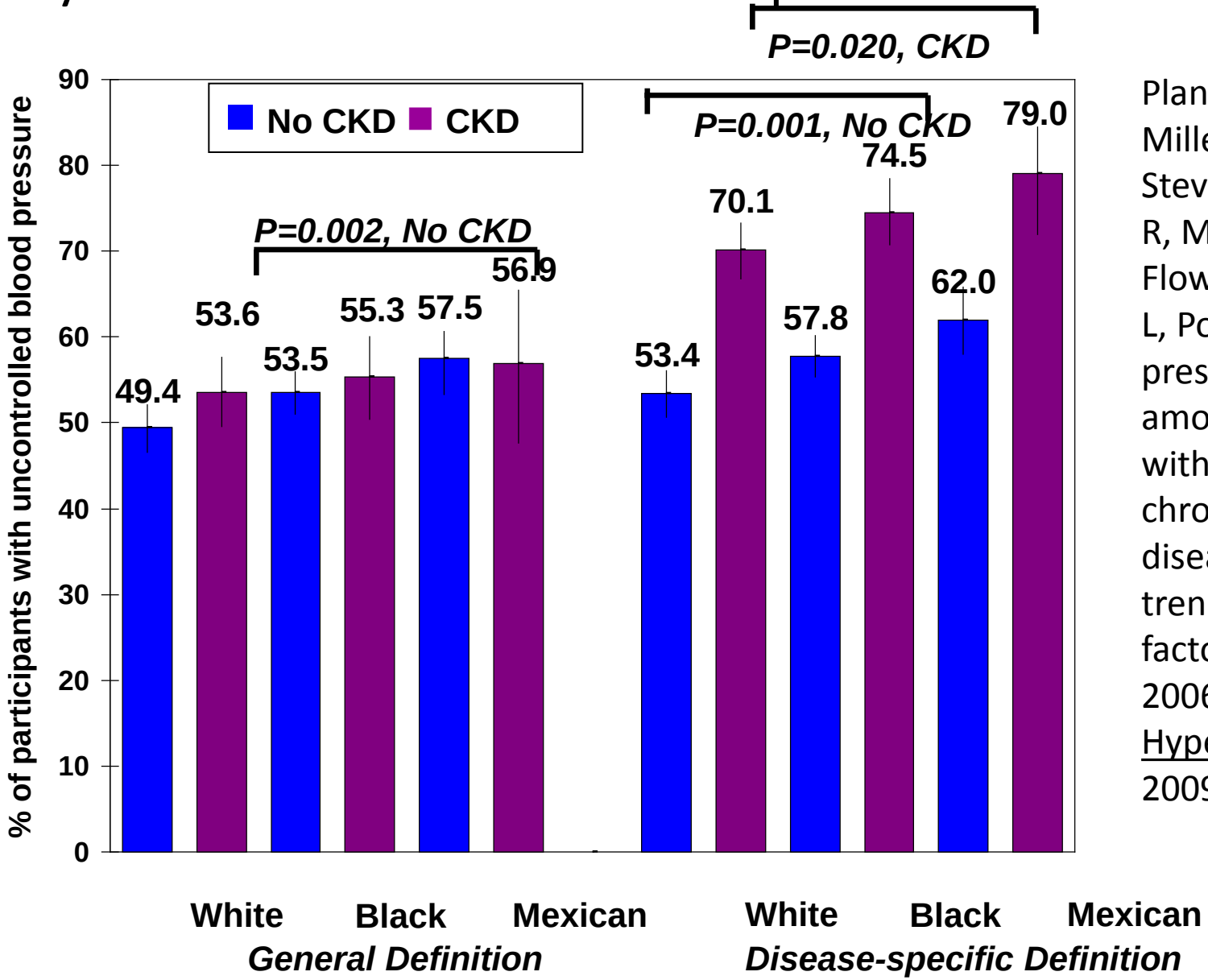


Banerjee T, Crews DC, Wesson DE, Tilea A, Saran R, Rios Burrows N, Williams DE, Powe NR; High Dietary Acid Load Predicts ESRD among Adults with CKD. *Journal of the American Society of Nephrology* 2015 : 26(7):1693-700

Factors contributing to Excess ESRD Incidence

- Biological
- Environmental
- Behavioral (e.g. lifestyle)
- **Quality/Adequacy of CKD care**

Minorities in the U.S. with Chronic Kidney Disease are more likely to have uncontrolled blood pressure

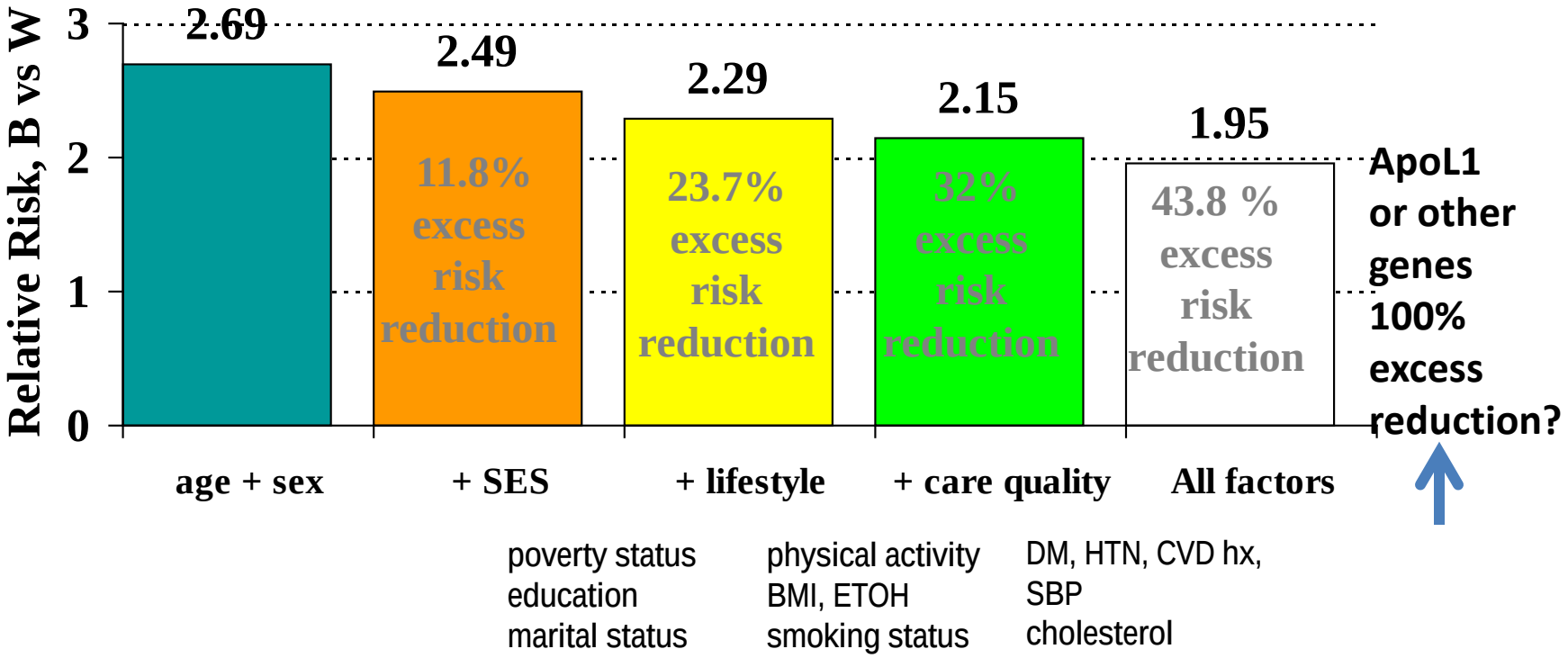


Plantinga LC, Miller ER, III, Stevens LA, Saran R, Messer K, Flowers N, Geiss L, Powe NR · Blood pressure control among persons without and with chronic kidney disease: U.S. trends and risk factors 1999-2006. Hypertension. 2009;54(1):47-56.

***Adjusted for survey year, age, sex, education, income, insurance, obesity, diabetes, and treatment.**

Socioeconomic Status, Lifestyle and Quality of Care Explains 44% of the 3-fold excess risk of CKD in African Americans vs Whites

NHANES II



Tarver-Carr M, Powe NR, Eberhardt M, LaVeist TA, Kington RS, Coresh J, Brancati F. Excess Risk of Chronic Kidney Disease among African-American versus White Subjects in the United States: A Population-Based Study of Potential Explanatory Factors.*Journal American Society Nephrology*. 2002;13:2363-70.

Questions to Ponder

- **How much does ApoL1 or other genes contribute to the disparity in ESRD incidence between African Americans and whites?**
  - How important is ApoL1 or other genes in comparison to other modifiable risk factors? (population attributable risk –incidence reduction if all unexposed)

Questions to Ponder

- How much does ApoL1 contribute to the disparity in ESRD incidence between African Americans and whites?
  - How important is ApoL1 in comparison to other modifiable risk factors? (population attributable risk –incidence reduction if all unexposed)
- **Are ApoL1 risk variants more susceptible to known kidney injury agents?**
  - Do APOL1 variants alter response to an environmental factor or to treatment?
- **Does knowing ApoL1 risk status lead to better health outcomes? What can be done?**
  - better blood pressure and diabetes control, avoidance of nephrotoxins (contrast media, medications, NSAIDS), less acidic diets
  - decision to be a live kidney donor and donor outcomes

Questions to Ponder - Mechanism?

- APOL1 has an endogenous function in podocyte necessary to resist environmental stress and maintain podocyte health?
  - Pathways are dysregulated in presence of two risk variants where clinical disease manifests with the introduction of an environmental stress.
- Gene/gene interactions?
  - Modifier loci may explain the differences in kidney pathologies between FSGS, HIVAN and hypertensive-attributed nephropathy.
- Gene/environment interactions?
  - Modifiable environmental second hits (viruses, antiviral pathway) may explain gaps between lifetime risks in individuals with same genetic background
- Risk in circulating APOL1 or APOL1 expressed in kidney?
- Apoptosis in podocytes?
  - biosynthesis, trafficking, ion channel properties, endocytosis, and effects on organellar structure and function

Insights from Studies Conducted in Diverse Race/Ethnic Groups

Trait	Findings
Breast cancer	Differences in Native American ancestry at the estrogen receptor locus led to discovery of a genetic variant that was protective against breast cancer in Latinas [11].
Heart failure	A post-hoc analysis of clinical trials of fixed-dose combination of hydralazine and isosorbide dinitrate suggested that black, but not white patients had a significant reduction in mortality compared to placebo [12].
Increased preterm birth rate	Exposures to endocrine disrupting chemicals such as bisphenol-A (BPA) are more common among minorities who live in low socioeconomic strata. BPA causes epigenetic alterations of the germ line resulting in increased preterm birth rate; these alterations can pass down to future generations [13].
Stevens-Johnson syndrome	The risk of carbamazepime-induced Stevens-Johnson syndrome due to HLA-B*1502 is highest in populations of Southeast Asian and East Asian ancestry [14].
Kidney disease	Genetic variants of *APOL1* have been associated with kidney disease in individuals of African ancestry whose ancestors lived in regions of Africa endemic with trypanosomiasis; these renal risk variants are largely absent in individuals of European or Asian ancestry [15].
Response to efavirenz	Blood levels and treatment response to this antiretroviral drug are influenced by individual ancestral make up, which can be accounted for by polymorphisms of cytochrome 2B6 and genetically defined ancestry [16,17].

Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NEWhite MJ, de Bruin DM, Greenblatt RM, Bibbins-Domingo K, Wu AH, Borrell LN, Gunter C, Powe NR, Burchard EG. Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. PLoS Med 2015; 12(12): e1001918. PLOS | MEDICINE

Factors contributing to Excess ESRD Incidence

- Biological
- Environmental
- Behavioral (e.g. lifestyle)
- **Quality/Adequacy of CKD care - downstream**

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

ARTICLE

The Timing of Specialist Evaluation in Chronic Kidney Disease and Mortality

Kraig S. Kinchen, MD, MSc; John Sadler, MD; Nancy Fink, MPH; Ronald Brookmeyer, PhD; Michael J. Klag, MD, MPH; Andrew S. Levey, MD; and Neil R. Powe, M.D., MPH, MBA

Background: Care for chronic renal failure involves management of complications and preparation for possible dialysis. Patients often are not evaluated by nephrologists in a timely manner.

Objective: To identify factors associated with late evaluation by a nephrologist and to assess whether late evaluation is associated with worse survival once patients develop end-stage renal disease (ESRD).

Design: National prospective cohort study.

Setting: 81 dialysis facilities throughout the United States.

Patients: 828 patients with new-onset ESRD.

Measurements: Time from first evaluation by a nephrologist to initiation of dialysis, classified as late (<4 months), intermediate (4 to 12 months), or early (>12 months); rate of death, from initiation of dialysis to an average of 2.2 years of follow-up; and demographic, clinical, and laboratory characteristics.

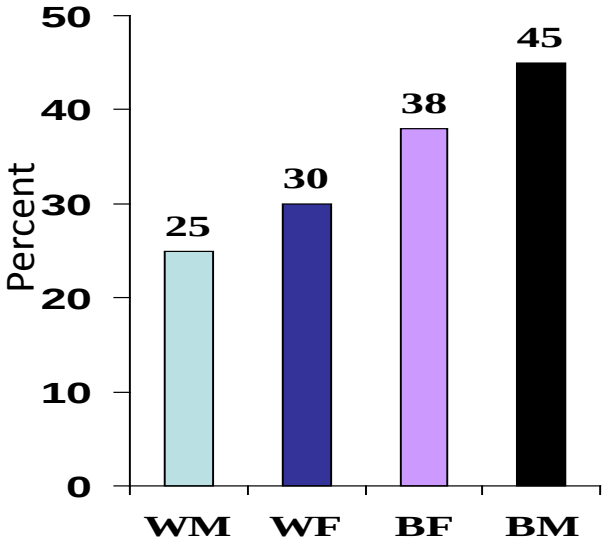
Results: After adjustment for potential confounders, late evaluation was more common among black men than white men (44.8% vs. 24.5%; $P < 0.05$), uninsured patients than insured patients (56.7% vs. 29.0%; $P < 0.05$) and patients with severe comorbid disease than those with mild comorbid disease (35.0% vs. 23.0%; $P < 0.05$). Compared with patients who had early evaluation, the risk for death was greater among patients evaluated late and was graded (hazard ratio, 1.3 [95% CI, 0.87 to 2.06] for patients with intermediate evaluation and 1.8 [CI, 1.21 to 2.61] for those with late evaluation) after adjustment for dialysis method, demographic characteristics, and socioeconomic status in Cox proportional hazards regression analysis. After additional adjustment for such factors as the presence and severity of comorbid conditions, the association remained graded (hazard ratio, 1.2 [CI, 0.73 to 1.82] for patients evaluated at an intermediate point and 1.6 [CI, 1.04 to 2.39] for those evaluated late).

Conclusions: Late evaluation of patients with chronic renal failure by a nephrologist is associated with greater burden and severity of comorbid disease, black ethnicity, lack of health insurance, and shorter duration of survival.

Ann Intern Med. 2002;137:478-486. www.annals.org
For author affiliations, see end of text.
See editorial comment on pp 542-543.

Over One Third of Black Dialysis Patients Receive a Late Evaluation by a Nephrologist

< 4 months before dialysis



Adjusted for age race, sex, education, lack of health insurance, Index of Coexistent Disease (ICED), marital status, and exercise status

CHOICE
CHOICE
CHOICE
CHOICE
CHOICE

Late evaluations are associated with poor preparation for dialysis[1]

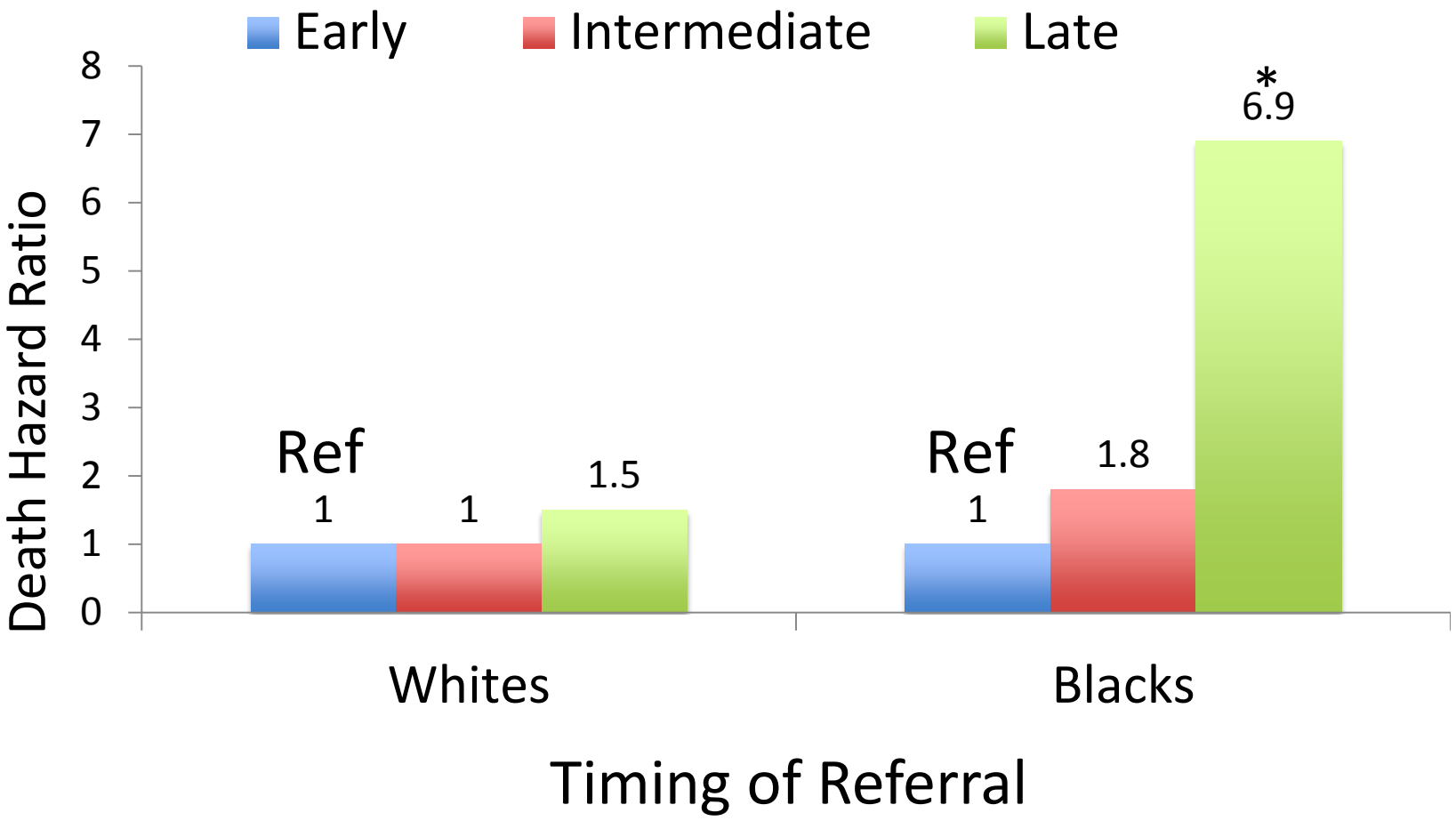
	Timing* of Evaluation			
	Early (n=399)	**Intermediate** (n=184)	**Late** (n=245)	**p**
Serum Albumin <3.6mg/l	60%	63%	78%	<0.01
Hematocrit <30%	56%	66%	68%	<0.01
Erythropoietin before dialysis	25%	31%	12%	<0.01

*time from first nephrologist evaluation to first dialysis <4 months (late); 4-12 months (intermediate); greater than 12 months (early)

Other studies: At start of dialysis, Blacks less likely to initiate dialysis with a fistula[2, 3] ,have hypertension controlled[4] and have anemia managed [5,6]

1. Kinchen KS, Sadler J, Fink N, Brookmeyer R, Klag, M, Levey A, Powe NR. The Timing of Specialist Evaluation in Chronic Kidney Disease and Mortality *Annals of Internal Medicine* 2002;137:479-486
2. USRDS Annual Data Report 2013
3. Healthy people 2020
4. Crews DC, Sozio SM, Liu Y, Coresh J, Powe NR. Inflammation and the paradox of racial differences in dialysis survival. J Am Soc Nephrol. 2011 Dec;22(12):2279-86..
5. Ifudu O, Dawood M, Iofel Y, Valcourt JS, Friedman EA. AKJD 33 (4): 728-733.
6. Slinin Y, Guo H, Gilbertson DT, Mau LW, Ensrud K, Rector T, Collins AJ, Ishani A. Meeting KDOQI guideline goals at hemodialysis initiation and survival during the first year. Clin J Am Soc Nephrol. 2010 Sep;5(9):1574-81.

Late specialty referrals resulted in worse mortality overall; up to 7-fold greater for Blacks



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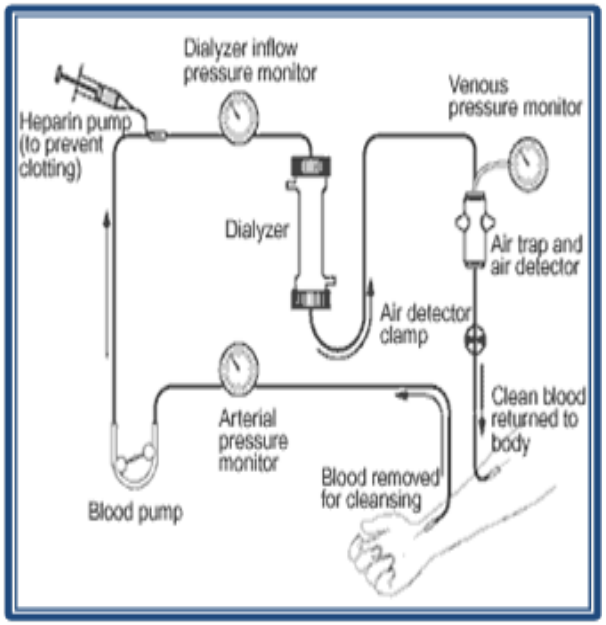
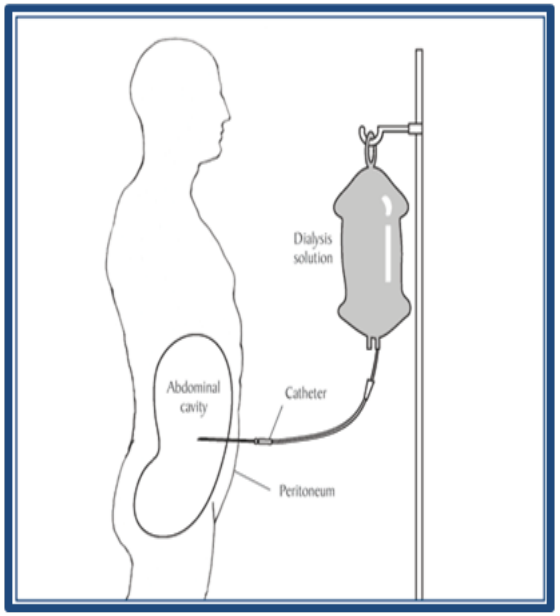
Poorly prepared patients miss opportunities to make informed treatment choices

Hemodialysis (HD)



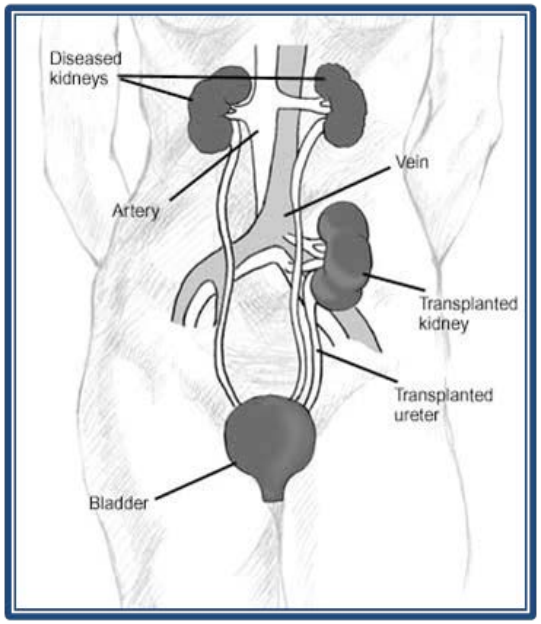
- In Center
- At home

Peritoneal Dialysis (PD)



- At home

Transplant



- Living
- Deceased

Graphics courtesy of National Kidney and Urologic Diseases Information Clearinghouse; NIDDK, NIH

Does choice of therapy matter?

- Debate on hemodialysis versus peritoneal dialysis
  - Risk of death in first year of treatment equivalent[1]
  - Hemodialysis may yield better long-term outcomes[1]
  - More frequent hemodialysis at home may be better[2]
  - Self-care modalities enhance quality of life
- Transplant yields better (up to 2-fold) length and quality of life and less cost compared to dialysis[3, 4]
  - Live donor transplant better[5]
  - Pre-emptive transplant better[6,7]

1 Jaar BG, Coresh J, Plantinga LC, Fink NE, Klag MJ, Levey AS, Levin NW, Sadler JH, Kliger A, Powe NR. Comparing risk for death with PD and hemodialysis. Ann Intern Med. 2005 ;143(3):174-83;
2 Culleton et al. JAMA. 2007 ;298(11):1291-9.; 3. Wolfe et al. N Engl J Med. 1999 Dec 2;341(23):1725-30. 4. Ojo et al. Am J Kidney Dis. 1994 Jul;24(1):59-64.;
5 Terasaki et al. N Engl J Med. 1995 Aug 10;333(6):333-6.; 6. Kasiske et al. J Am Soc Nephrol. 2002 May;13(5):1358-64;
7. Mange et al. Engl J Med. 2001 Mar 8;344(10):726-31.

African Americans versus Whites

- Less likely to be waitlisted and transplanted[1]
- Less likely to receive live kidney transplants[2]
- Less likely to have knowledge of kidney replacement therapies[3]
- Less knowledge of transplant prior to dialysis initiation[4]
- Lower health literacy – health literacy associated with transplantation[5]
- Less knowledgeable when being evaluated for transplant; when knowledge is accounted for race differences in transplant evaporate[6]

1. United States Renal Data System 2015 Annual Report
2. Gore JL, Danovitch GM, Litwin MS, Pham PTT, Singer JS. Disparities in the Utilization of Live Donor Renal Transplantation. AJT 2009 9:1124-1133
3. Finkelstein FO. Perceived knowledge of CKD and ESRD. Kidney International (2008) 74, 1178-1184
4. Ayanian et al. The Effect of Patient's Preferences on Racial Differences in Access to Renal Transplantation. *NEJM* 1999; 341 1661-1669
5. Grubbs V, Gregorich SE, Perez-Stable EJ, Hsu C. Health literacy and access to kidney transplantation. Clin J Am Soc Nephrol 4: 195-200, 2009
6. Waterman AD et al. Modifiable Patient Characteristics and Racial Disparities in Evaluation Completion and Living Donor Transplant. CJASN ePress. Published on March 28, 2013 as doi: 10.2215/CJN.08880812

Summary and Conclusions

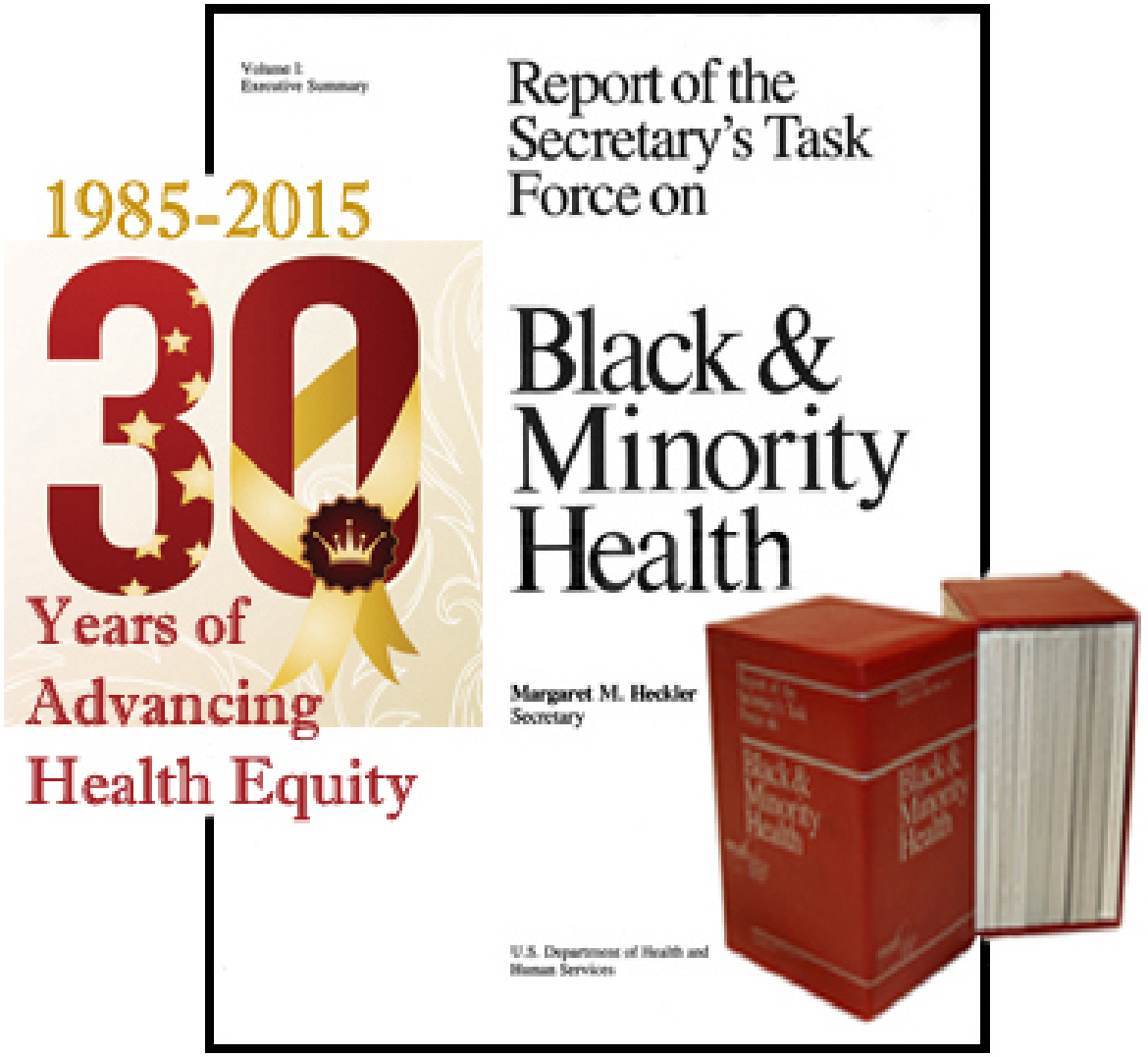
- African American patient with late presentation for care, poor preparation for ESRD, urgent hemodialysis initiation
- Treating disease at end-stage is costly, both personally and financially, and limits access to optimal therapies
- Biologic, socioeconomic, behavioral & clinical determinants conspire to compromise health & healthcare
- Need to develop and rigorously test interventions created to address these determinants to human health
  - Learn how to pre-empt illness through molecular knowledge, therapeutics and behavioral interventions
- Disparities research allows examination of complex interactions that contribute (often unequally) to health

Summary and Conclusions

- A growing proportion of Americans are not fully benefiting from clinical and biomedical advances since racial and ethnic minorities make up ~ 40% of the United States population[1]
- Most physicians and scientists are informed by research extrapolated from a largely homogenous population[1]
- Ignoring diversity of US population is a missed scientific opportunity to understand factors that lead to disease or health[1]
- US biomedical research and study populations must better reflect the country's changing demographics. [1]
- **Science on disparities, clinical care with diverse patients, and education about disparities enhances all of Medicine and human health.**

1. Oh SS, Galanter J, Thakur N, Pino-Yanes M, Barcelo NE, White MJ, de Bruin DM, Greenblatt RM, Bibbins-Domingo K, Wu AH, Borrell LN, Gunter C, Powe NR, Burchard EG. Diversity in Clinical and Biomedical Research: A Promise Yet to Be Fulfilled. PLoS Med 2015; 12(12): e1001918.

THANK YOU!


Volume I:
Executive Summary
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Years of Advancing Health Equity
Margaret M. Heckler
Secretary
U.S. Department of Health and Human Services