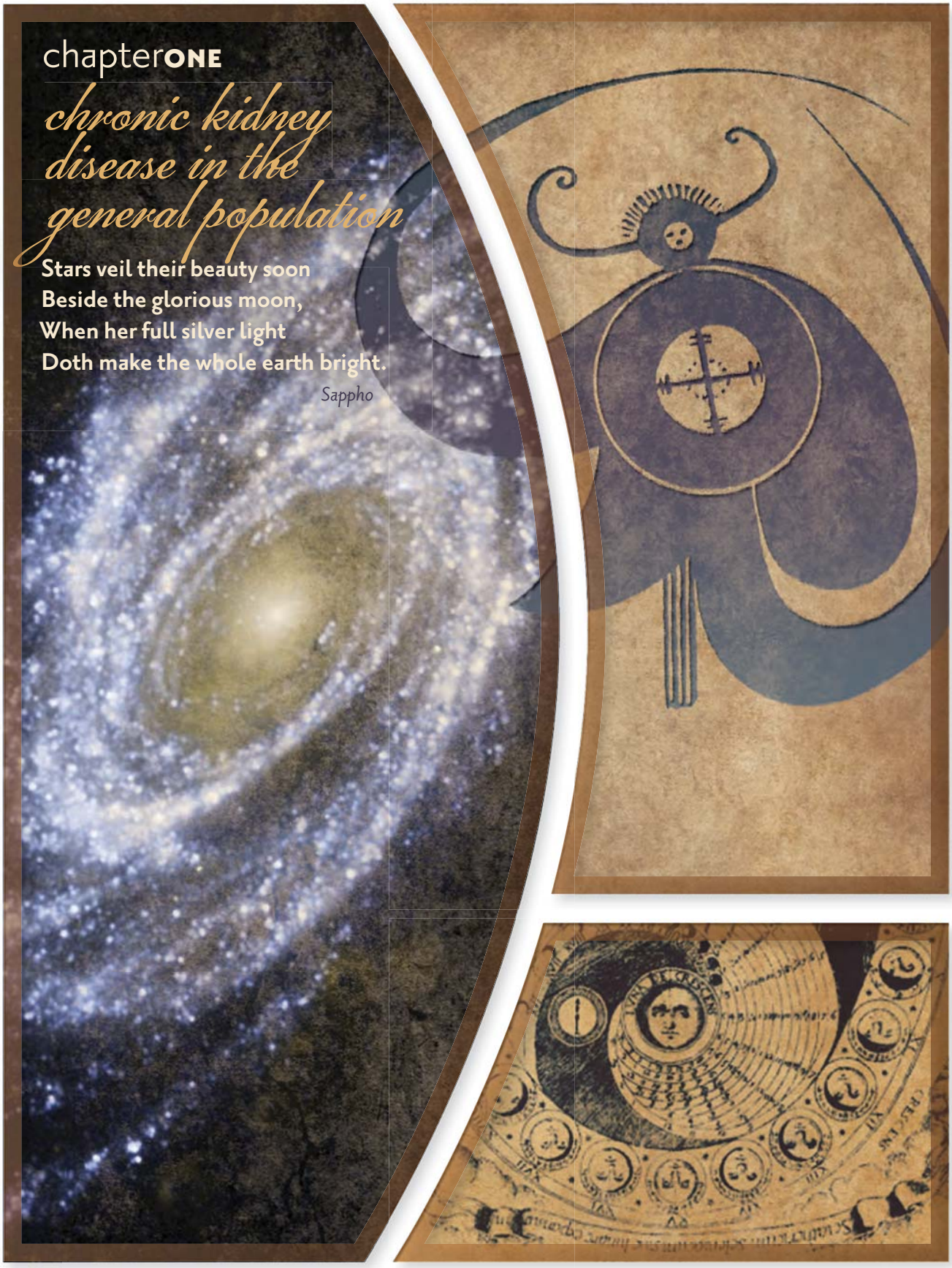
chapter**ONE**

chronic kidney disease in the general population

Stars veil their beauty soon
Beside the glorious moon,
When her full silver light
Doth make the whole earth bright.

Sappho



In this chapter we use data from the National Health and Nutrition Examination Survey (NHANES), a valuable source of information for assessing disease burden and high-risk subsets among representative U.S. adults. On the next page we begin by showing the overall burden and interactions of diabetes, congestive heart failure, and CKD — three interrelated chronic diseases. Data vary only slightly based on the estimating equation used to define CKD: the older MDRD Study equation, which underestimates glomerular filtration rates (eGFRs) over 60 ml/min/1.73 m^2, compared to the newer CKD-EPI equation, which partially addresses this issue.

The prevalence of diabetes in the U.S. continues to grow, reaching 7.7 percent of the general population in 2003–2006. The prevalence of congestive heart failure has also increased, to 2.5 percent.

Estimating the CKD population is more challenging. While a decline in kidney function is common in the elderly, this population also has the greatest burden of chronic disease, confounding the question of whether CKD is simply part of aging or a true chronic disease coexisting with others such as diabetes and hypertension. In any case, its implications are considerable.

Compared to the MDRD equation, the new CKD-EPI equation for estimating GFR identifies, in populations younger than 60, a greater number of patients with GFRs above 60 ml/min/1.73 m^2, and has greater sensitivity to detect CKD, though similar specificity. Use of CKD-EPI thus shows a greater burden of comorbidity among patients with eGFRs less than 60 ml/min/1.73 m^2, as the placement of healthier patients into the above-60 group leaves behind a denominator of patients with more chronic disease. For the same reason, use of the CKD-EPI equation also shows a greater burden of biochemical abnormalities among those patients still classified as having lower eGFRs.

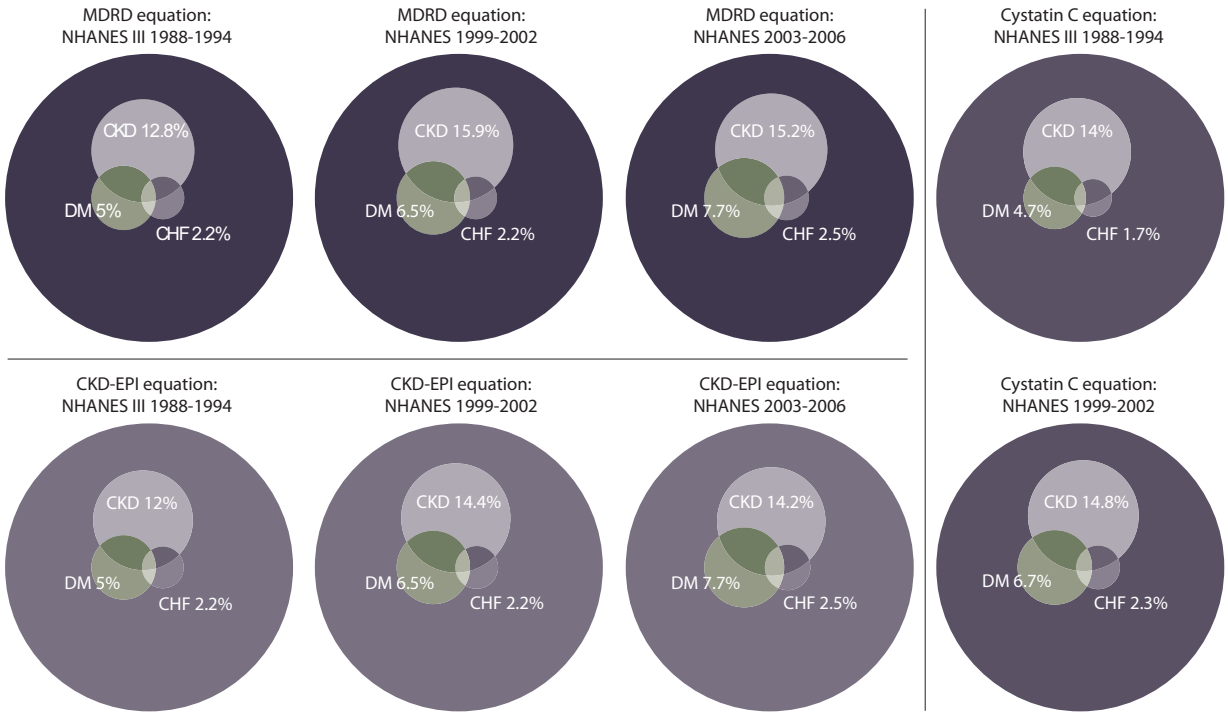
With potent mortality classification systems, "normal" values should accurately predict survival (high specificity) and "abnormal" values should accurately predict death (high sensitivity); in public health settings, classification based on a threshold with the highest combined sensitivity and specificity is a logical choice. We evaluate sensitivity and specificity of different eGFR and ACR thresholds for discriminating death or survival. For the cystatin C-based eGFR, a threshold value of 90 ml/min/1.73 m^2 matches to a threshold of 85 with the creatinine-based MDRD equation, a value of 91 with the CKD-EPI equation, and a urinary albumin-creatinine ratio of 8 mg/g.

These data demonstrate that the equation used to estimate GFR has an important impact on the prediction of death. The CKD-EPI equation provides a more consistent pattern of mortality rates than does the MDRD equation. As it addresses the issue of falsely low eGFR measurements (particularly in younger populations), and improves the predictive value of eGFRs, the CKD-EPI equation should be considered to replace the older MDRD equation. Additionally, socioeconomic factors should be addressed in future assessments of CKD and its predictive power related to death and other outcomes.

Exploring the implications of CKD, diabetes, and cardiovascular disease in the general population, this chapter sets the stage for Chapter Two, in which we discuss the implications of CKD in datasets that are less well defined in terms of biochemical data, but that provide extensive information on morbidity, interventions, and costs not contained in the NHANES data or other samples.

Figure 1.1 ; see page 166 for analytical methods. *NHANES participants age 20 & older.*

1.1 **Distribution of NHANES participants with diabetes, congestive heart failure, & markers of CKD, with GFR estimated by MDRD, CKD-EPI, & cystatin C equations**



1a*i* **Prevalence & odds of CKD in NHANES 1999–2006 participants, by method used to estimate GFR, CKD stage, age, gender, race/ethnicity, & risk factor (percent of participants)**

	eGFR MDRD					eGFR CKD-EPI					eGFR cystatin C				
	Stg 1	Stg 2	Stg 3	Stgs 4-5	OR	Stg 1	Stg 2	Stg 3	Stgs 4-5	OR	Stg 1	Stg 2	Stg 3	Stgs 4-5	OR
20-39	3.6	1.8	0.5	0.1*	ref	4.7	0.7	0.2*	0.1*	ref	5.5	1.3*	0.8*	0.2*	ref
40-59	3.3	3.9	4.2	0.2	1.6	4.9	2.5	2.0	0.2	1.4	3.2	3.6	3.3	0.3*	1.1
60+	2.3	8.4	26.3	1.8	5.9	2.4	8.6	24.3	2.1	5.8	2.8	8.8	21.4	2.0	3.6
Male	2.7	4.1	6.0	0.5	ref	3.5	3.4	5.2	0.6	ref	2.9	3.7	5.5	0.8	ref
Female	3.7	4.1	9.4	0.5	1.4	5.0	3.0	7.4	0.6	1.3	5.0	4.0	7.2	0.5	1.4
Non-Hispanic white	2.2	4.1	9.2	0.5	ref	3.2	3.3	7.4	0.6	ref	3.0	4.0	7.5	0.6	ref
Non-Hispanic Af Am	5.7	4.2	4.8	1.1	1.1	6.3	3.4	4.9	1.2	1.3	8.6	4.1	4.1	1.5	1.3
Other	6.2	3.9	3.3	0.5*	1.2	7.5	2.6	2.6	0.4	1.3	5.1	3.1	3.0	0.4*	1.0
Self-reported diabetes	8.9	12.8	19.4	2.7	2.5	11.8	10.2	17.0	3.1	2.5	7.6	11.4	15.0	2.9	1.9
Self-reported hypertension	4.1	7.0	16.7	1.6	1.8	5.4	5.9	14.6	1.7	1.8	3.6	8.2	14.9	2.1	2.0
Self-reported CVD	2.8	8.6	27.9	3.8	2.0	3.3	8.7	25.9	4.3	2.1	1.9*	10.2	25.8	4.2	2.3
Current smoker	4.4	3.7	3.6	0.5	1.1	5.9	2.3	2.4	0.5	1.1	6.2	4.8	4.3	0.6*	1.8
Obese (BMI ≥30)	3.9	5.6	8.0	0.6	1.1	5.5	4.2	6.6	0.6	1.1	3.7	6.1	8.0	0.6	1.2
All	3.2	4.1	7.8	0.5		4.3	3.2	6.3	0.6		4.0	3.9	6.4	0.6	

1b*i* **Sensitivity & specificity of different population characteristics for identifying eGFR <60 ml/min/1.73 m² & urinary ACR ≥30 mg/g**

	eGFR MDRD <60		eGFR CKD-EPI <60		eGFR cystatin C <60		ACR ≥30 mg/g	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Age 20+	100.0		100.0		100.0		100.0	
Age 50+	86.7	66.1	94.6	65.7	91.5	44.0	60.5	64.3
Age 50+, or age <50 with DM or HTN	92.1	55.8	98.0	55.4	96.5	36.3	73.3	54.9
Age 50+, or age <50 with DM, HTN, or CVD	92.6	55.1	98.6	54.7	97.1	36.0	73.9	54.1
Age 60+	72.8	82.3	85.3	82.3	84.4	55.2	44.9	80.5
Age 60+, or age <60 with DM or HTN	86.1	65.8	94.6	65.5	95.3	43.3	67.6	65.1
Age 60+, or age <60 with DM, HTN, or CVD	86.8	64.5	95.4	64.2	96.2	42.8	68.6	63.7

Data on the different stages of CKD among NHANES participants show that, using a single creatinine-based eGFR and the MDRD equation, 3.2, 4.1, 7.8, and 0.5 percent, respectively, have CKD of Stages 1, 2, 3, and 4–5. With the CKD-EPI equation, the corresponding proportions are 4.3, 3.2, 6.3, and 0.6 percent, indicating that CKD-EPI tends to give a higher eGFR estimate than the MDRD equation. When using a single eGFR based on cystatin C, the corresponding proportions are 4.0, 3.9, 6.4, and 0.6 percent. Multivariate associations of CKD for all three eGFR methods include older age, female gender, self-reported diabetes, hypertension, and cardiovascular disease.

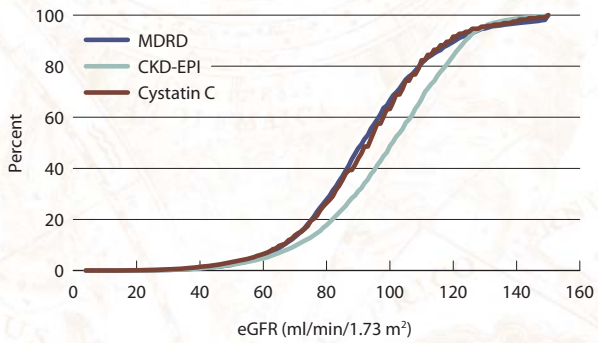
Table 1.b shows the sensitivity and specificity of different screening strategies to identify eGFR values less then 60 ml/min/1.73 m² or albumin creatinine ratio (ACR) values of 30 mg/g and above. In general, the screening strategies show greater sensitivity for detecting eGFRs less than 60 ml/min/1.73 m² with the CKD-EPI equation than with the MDRD or cystatin C methods, while specificity values tend to be similar across all three methods. ⁜ **Tables 1.a–b;** see page 166 for analytical methods.

*NHANES 1999–2006 participants age 20 & older. *Estimate not reliable.*

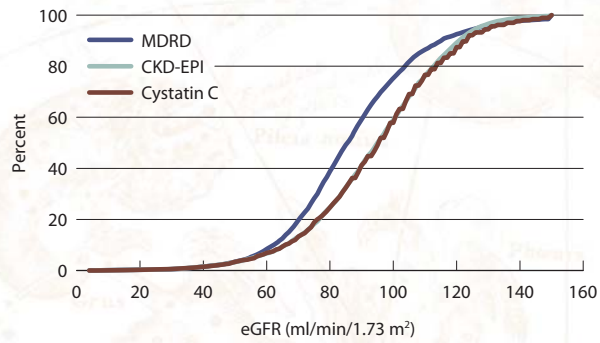
CKD stage markers

1. eGFR ≥90, albumin/creatinine ratio (ACR) ≥30 mg/g
2. eGFR 60–89, ACR ≥30 mg/g
3. eGFR 30–59
4. eGFR 15–29
5. eGFR <15 (dialysis patients excluded from analyses)

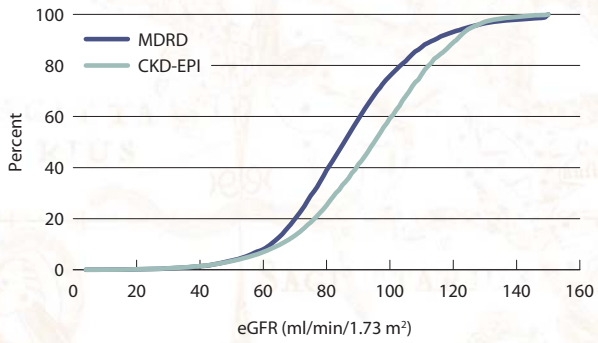
1.2*i* **Cumulative distribution curves of NHANES 1988–1994 participants, by eGFR & method used to estimate GFR**

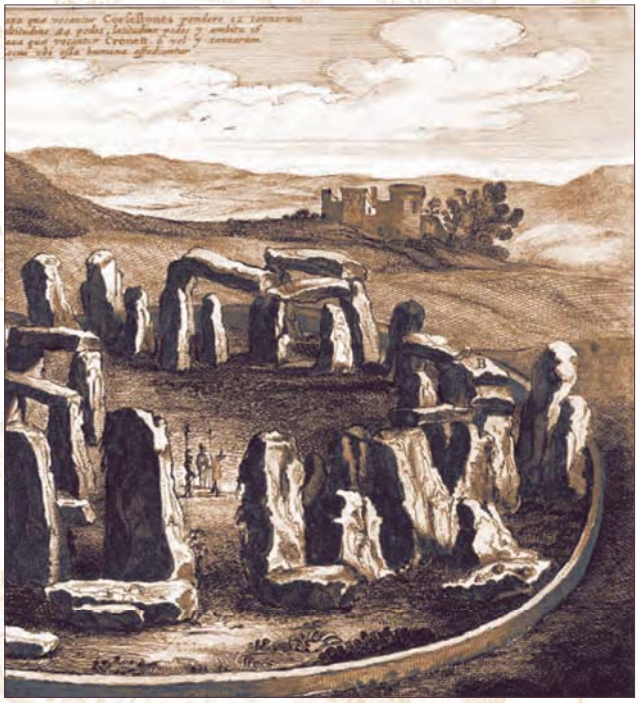


1.3*i* **Cumulative distribution curves of NHANES 1999–2002 participants, by eGFR & method used to estimate GFR**



1.4*i* **Cumulative distribution curves of NHANES 2003–2006 participants, by eGFR & method used to estimate GFR**





In cumulative frequency distributions of eGFR in U.S. adults, creatinine-based CKD-EPI and cystatin C methodologies for eGFR calculation yield higher estimates of GFR than those achieved when using the creatinine-based MDRD method. ⁜ **Figures 1.2–4**; see page 166 for analytical methods. *NHANES participants age 20 & older.*

Diabetes, hypertension, and cardiovascular disease are much more common in persons with CKD than in those without. In general, there is a trend towards higher prevalence estimates with rising CKD stage; this is particularly true in patients with hypertension and cardiovascular disease. **TABLE I.C;** see page 166 for analytical methods. *NHANES 1999–2006 participants age 20 & older. *Estimate not reliable.*

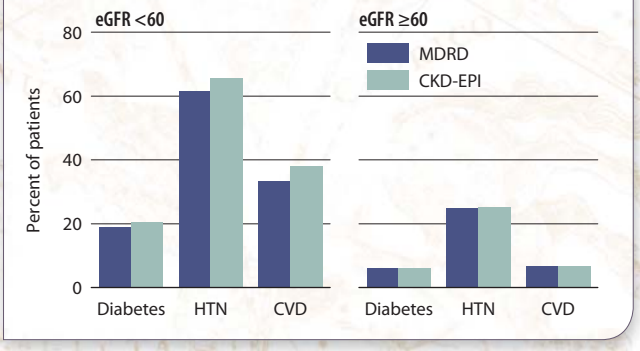
CKD stage markers

1. eGFR ≥90, albumin/creatinine ratio (ACR) ≥30 mg/g
2. eGFR 60–89, ACR ≥30 mg/g
3. eGFR 30–59
4. eGFR 15–29
5. eGFR <15 (dialysis patients excluded from analyses)

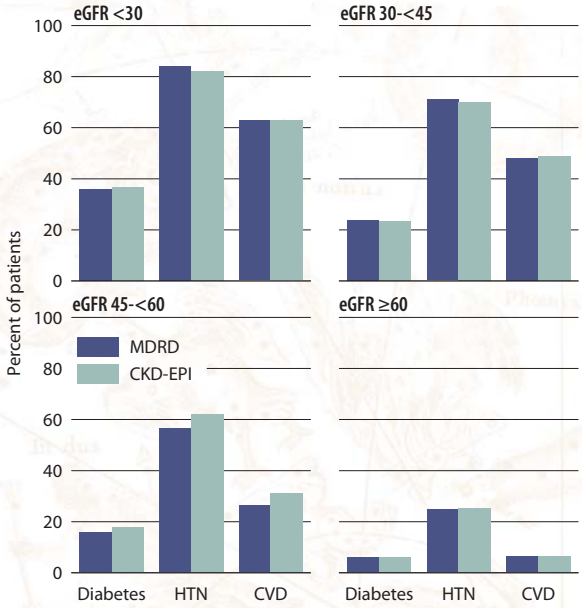
I.C*i* Prevalence (%) of diabetes, hypertension, & cardiovascular disease in NHANES 1999–2006 participants, by age, gender, race/ethnicity, CKD status, & method used to estimate GFR

	Diabetes		Hypertension		Cardiovascular disease	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
Age 60+	16.1	16.1	54.5	54.5	26.1	26.1
Non-CKD	11.6	11.6	48.7	48.6	18.5	18.1
Stage 1	36.2	36.5	62.9	63.1	28.3	22.1
Stage 2	24.1	23.4	57.8	57.8	30.6	33.1
Stage 3	19.2	19.5	63.9	65.1	36.6	38.1
Stages 4–5	39.8	39.2	83.6	81.9	72.3	69.6
Male	7.2	7.2	26.5	26.5	9.5	9.5
Non-CKD	4.6	4.6	22.6	22.7	6.5	6.5
Stage 1	26.8	26.2	38.3	36.5	10.8	9.5
Stage 2	27.1	27.3	49.7	54.5	23.0	27.0
Stage 3	18.9	20.9	59.1	62.5	38.0	41.9
Stages 4–5	33.7	33.9	83.3	79.8	59.8	59.7
Female	7.3	7.3	29.2	29.2	8.3	8.3
Non-CKD	4.8	5.0	24.0	24.4	5.2	5.3
Stage 1	14.9	15.7	34.1	35.2	5.5	4.9
Stage 2	17.7	18.2	46.8	49.9	14.3	20.8
Stage 3	17.2	17.9	60.3	65.2	27.4	31.6
Stages 4–5	38.1	39.6	84.8	84.4	65.6	65.9
Non-Hispanic white	6.4	6.4	28.7	28.7	9.8	9.8
Non-CKD	4.3	4.4	24.1	24.4	6.4	6.5
Stage 1	19.0	18.3	35.3	35.1	9.6	7.2
Stage 2	18.7	19.7	46.0	49.6	20.0	26.8
Stage 3	15.8	16.5	58.6	62.3	31.7	36.3
Stages 4–5	34.2	34.2	81.4	80.4	68.8	67.4
Non-Hispanic Af Am	10.8	10.8	35.3	35.3	8.8	8.8
Non-CKD	6.5	6.4	29.5	29.3	5.3	5.2
Stage 1	23.6	22.6	46.7	44.5	10.4	9.5
Stage 2	36.2	39.4	62.3	68.5	19.6	22.4
Stage 3	34.6	34.9	81.1	83.9	36.3	37.7
Stages 4–5	34.5	36.0	92.1	89.3	51.7	49.3
Other race	8.5	8.5	19.6	19.6	4.8	4.8
Non-CKD	5.7	5.7	16.0	16.1	3.7	3.7
Stage 1	18.7	21.2	30.2	32.1	3.0*	4.3
Stage 2	28.7	26.3	48.8	52.8	10.1	10.0
Stage 3	26.6	33.0	55.6	62.7	22.9	26.2
Stages 4–5	46.8	56.0	84.2	79.6	52.4	62.0
All	7.2	7.2	27.9	27.9	8.9	8.9
Non-CKD	4.7	4.8	23.3	23.6	5.8	5.9
Stage 1	19.8	19.8	35.8	35.7	7.7	6.7
Stage 2	22.2	22.8	48.1	52.2	18.4	24.0
Stage 3	17.8	19.1	59.9	64.1	31.4	35.7
Stages 4–5	36.0	36.9	84.1	82.2	62.8	63.0

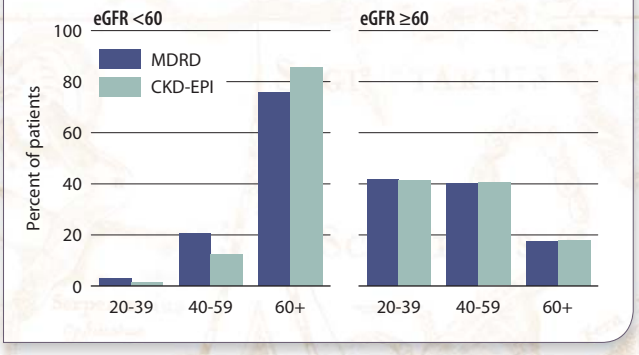
1.5*i* **Prevalence of comorbidity in NHANES 1999–2006 participants, by risk factor, eGFR, & method used to estimate GFR**



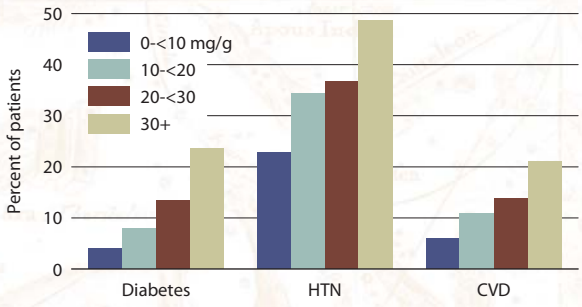
1.6*i* **Prevalence of comorbidities in NHANES 1999–2006 participants, by risk factor, expanded eGFR categories, & method used to estimate GFR**



1.7*i* **Distribution of NHANES 1999–2006 participants, by risk factor, eGFR, & method used to estimate GFR**



1.8*i* **Prevalence of comorbidity in NHANES 1999–2006 participants, by risk factor & albumin/creatinine ratio**



With both creatinine-based MDRD and CKD-EPI estimates, the prevalence of diabetes, hypertension, or cardiovascular disease is noticeably higher in subjects with eGFRs below 60 ml/min/1.73 m² than among those whose eGFR equals or exceeds 60. Approximately 61–66 percent of NHANES participants with an eGFR less than 60, for example, have hypertension, compared to 25 percent in those with an eGFR of 60 or greater, and the prevalence of cardiovascular disease is more than five times greater in those with advanced CKD, at 33–38 versus 6–7 percent.

The prevalence of disease rises with CKD severity. In participants with eGFRs less than 30, 30–<45, and 45–<60, for example, 37, 24, and 17 percent report having diabetes, compared to 6.1 percent of those with an eGFR of 60 or above. And in participants with an eGFR less than 30 ml/min/1.73 m², approximately 83 percent have hypertension and 63 percent have cardiovascular disease, compared to 25 and 7.0 percent, respectively, of participants with an eGFR of 60 or greater.

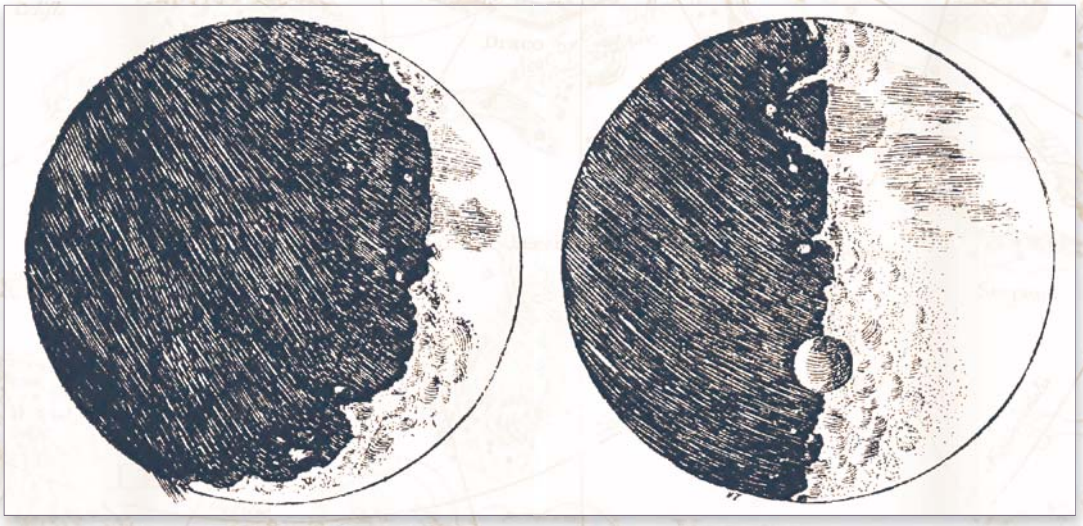
More than three of four NHANES participants with an eGFR less than 60 ml/min/1.73 m² are age 60 or older, while only 3.0 percent are age 39 or younger.

The prevalence of comorbid illness among NHANES participants rises with albumin/creatinine ratio (ACR). Four percent of those with an ACR less than 10 mg/g have diabetes; this rises to 24 percent of those whose ACR is 30 or greater. Hypertension and cardiovascular disease are evident in 23 and 6.1 percent of individuals with an ACR below 10, compared to 49 and 21 percent in those with an ACR of 30 or greater. ÷ **Figures 1.5–8;** see page 166 for analytical methods. *NHANES 1999–2006 participants age 20 & older.*

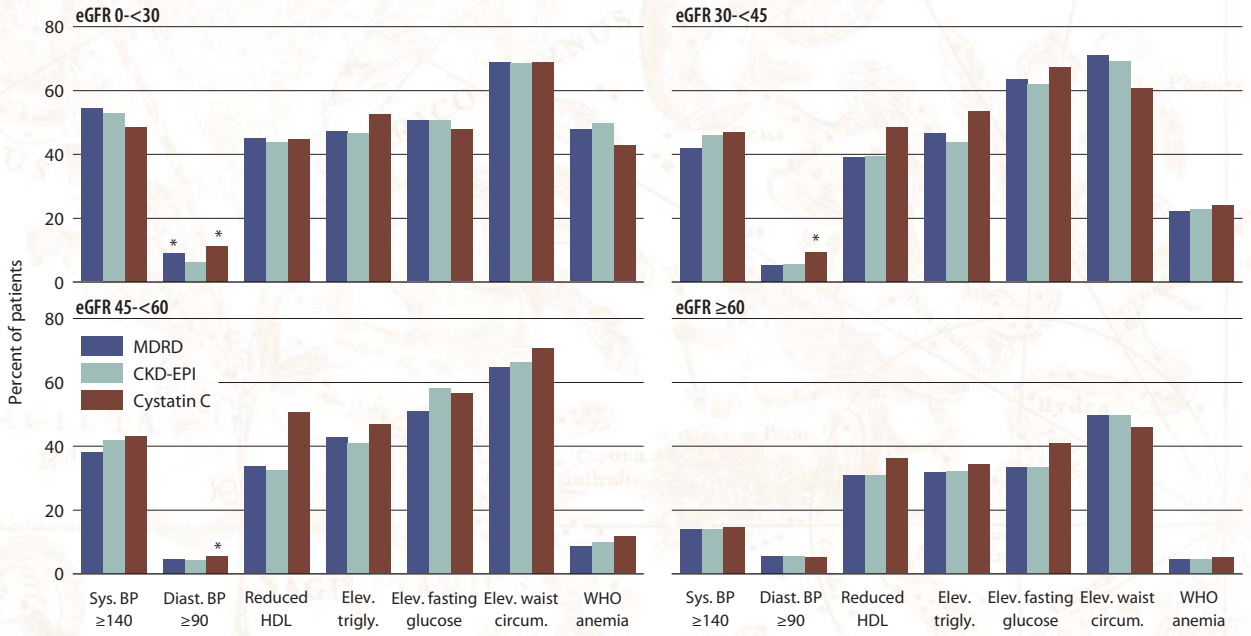
Regarding the prevalence of clinical and laboratory abnormalities in subjects with and without an eGFR less than 60 ml/min/1.73 m^2, there are associations with the following abnormalities: high potassium, uric acid, and phosphorus, reduced HDL, and low hemoglobin levels. ⁜ **Table 1.d;** see page 166 for analytical methods. *NHANES 1999–2006 participants age 20 & older; for cystatin C, NHANES 1999–2002 participants. *Estimate not reliable; **significant (p<0.01).*

1d **Abnormalities of selected clinical & biochemical parameters in NHANES participants, by eGFR & method used to estimate GFR (percent of participants)**

	MDRD (NHANES 1999–2006)			CKD-EPI (NHANES 1999–2006)			Cystatin C (NHANES 1999–2002)		
	eGFR <60	eGFR ≥60	OR	eGFR <60	eGFR ≥60	OR	eGFR <60	eGFR ≥60	OR
Potassium ≥4.5 mmol/l	23.0	8.6	2.1**	25.4	8.7	2.3**	24.1	11.2	1.9**
Bicarbonate ≤20.5 mmol/l	6.3	5.1	2.0**	6.9	5.1	2.8**	10.2	8.3	2.0**
Uric acid ≥7.7 mg/dl	20.6	5.3	5.1**	22.9	5.4	5.8**	24.4	6.2	5.0**
Calcium ≤8.9 mg/dl	6.9	6.9	1.0	7.6	6.9	1.1	10.6	10.3	1.2
Phosphorus ≥4.7 mg/dl	7.9	4.6	2.6**	7.5	4.7	2.5**	7.8*	3.4	4.1**
Systolic BP ≥140 mmHg	39.8	13.9	1.2	43.8	14.0	1.2	44.6	14.7	1.2
Diastolic BP ≥90 mmHg	5.1	5.7	0.8	4.6	5.7	0.7	7.1	5.2	1.1
Systolic BP ≥130 mmHg	58.3	27.1	1.1	63.3	27.2	1.2	63.1	26.9	1.2
Diastolic BP ≥85 mmHg	21.1	23.4	0.9	18.6	23.5	0.8	21.7	25.1	0.7
Reduced HDL	35.5	30.9	1.3**	35.1	31.0	1.3**	49.8	36.1	2.1**
Elevated triglycerides	43.7	31.8	1.3	42.1	32.1	1.1	49.2	34.4	1.5
Elevated fasting glucose	53.2	33.3	1.0	58.5	33.3	1.2	58.2	41.0	1.2
Elevated waist circumference	66.3	49.6	0.9	67.2	49.8	0.9	68.4	45.9	1.2
WHO anemia	14.2	4.6	3.1**	16.5	4.6	3.7**	17.4	5.1	4.8**



1.9*i* **Abnormalities of selected clinical & biochemical parameters in NHANES 1999–2006 participants, by expanded eGFR categories & method used to estimate GFR**



Regarding associations between selected clinical and biochemical abnormalities, the proportions of patients with each abnormality are broadly independent of the method used to estimate GFR. Conditions associated with low eGFR include: elevated systolic blood pressure, reduced HDL, elevated triglycerides, elevated fasting glucose, and elevated waist circumference. ⁜ **Figure 1.9;** see page 166 for analytical methods.
*NHANES 1999–2006 participants age 20 & older; for cystatin C, NHANES 1999–2002 participants. *Estimate not reliable.*

Analysis definitions

1. Hypertension defined as blood pressure ≥130/≥80 for those with CKD and diabetes; otherwise ≥140/≥90, or self-reported treatment for hypertension.
2. Awareness and treatment are self-reported. Control defined as <130/<80 for those with CKD and diabetes; otherwise <140/<90.
3. Hypercholesterolemia based on elevated LDL following Adult Treatment Panel III (ATP III) guidelines, with CKD considered a risk equivalent for chronic heart disease, self-reported treatment, or self-reported dieting to lower cholesterol.
4. Awareness and treatment self-reported. Control defined as meeting the National Cholesterol Education Program (NCEP) ATP III LDL target: <100 mg/dl (high risk), <130 mg/dl (moderate risk), or <160 mg/dl (low risk).
5. HDL cholesterol classified according to ATP III guidelines.
6. Total cholesterol classified according to ATP III guidelines.
7. Glycohemoglobin classified according to American Diabetes Association guidelines.

CKD stage markers

1. eGFR ≥90, albumin/creatinine ratio (ACR) ≥30 mg/g
2. eGFR 60–89, ACR ≥30 mg/g
3. eGFR 30–59
4. eGFR 15–29
5. eGFR <15 (dialysis patients excluded from analyses)

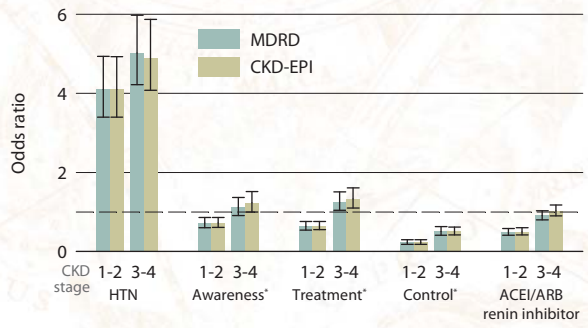
1e **Awareness, treatment, & control of hypertension, hypercholesterolemia, HDL cholesterol, & diabetes, by CKD stage & method used to estimate GFR (percent of NHANES participants)**

	Non–CKD		Stages 1–2		Stages 3–4	
	MDRD	CKD-EPI	MDRD	CKD-EPI	MDRD	CKD-EPI
Hypertension, by current hypertensive status[1]						
Non-hypertensive status	74.4	73.8	36.2	35.6	19.6	15.6
Hypertensive (measured/treated)	25.7	26.2	63.9	64.4	80.5	84.4
Control of hypertension among hypertensive patients[2]						
Unaware	30.9	31.0	36.1	36.2	25.5	23.9
Aware, not treated	11.3	11.1	14.2	13.8	6.1	6.0
Aware, treated, uncontrolled	23.8	24.2	39.1	39.4	48.3	50.5
Aware, treated, controlled	34.0	33.7	10.6	10.5	20.0	19.5
Hypercholesterolemia (LDL): LDL cholesterol[3]						
Within ATP-III target LDL range	66.3	65.6	52.1	51.2	20.2	20.4
Hypercholesterolemic (measured or treated)	33.7	34.4	47.9	48.8	79.8	79.6
Control of hypercholesterolemia (LDL) among participants with hypercholesterolemia (LDL)[4]						
Unaware	34.3	34.6	32.3	32.6	44.1	43.6
Aware, not treated	9.1	9.3	7.7	7.8	8.4	7.2
Aware, treated, uncontrolled	21.6	22.2	29.2	29.2	29.6	27.7
Aware, treated, controlled	35.0	33.9	30.9	30.3	17.9	21.5
HDL cholesterol in ATP III target range[5]						
HDL <40 mg/dl (ATP III target)	19.2	19.1	22.7	22.6	18.5	18.9
HDL 40 mg/dl or higher (at/above ATP III target)	80.8	80.9	77.3	77.4	81.5	81.2
Total cholesterol[6]						
<200 (desirable)	52.1	52.0	47.7	48.0	47.6	48.8
200–239 (borderline high)	31.7	31.8	31.3	30.9	31.8	31.6
240+ (high)	16.1	16.3	21.1	21.2	20.6	19.6
Control of diabetes among diabetic patients[7]						
Glycohemoglobin <7% (controlled)	51.3	51.0	36.1	37.2	53.5	53.4
Glycohemoglobin 7% or higher (uncontrolled)	48.7	49.0	63.9	62.8	46.5	46.6

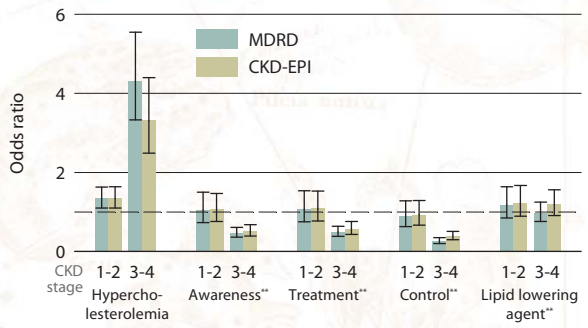
Here we use NHANES data from 1999–2006 to evaluate awareness, treatment, and control of disease conditions, using CKD stages defined with two creatinine-based methodologies to estimate GFR. With the MDRD method, 80.5 percent of participants with CKD of Stages 3–4 have hypertension; only 20 percent, however, are aware of their condition and on a successful treatment regime. With the CKD-EPI method, 84.4 percent of Stage 3–4 participants have hypertension, while 19.5 percent are aware of their condition and receiving adequate treatment. Among patients with earlier stages of CKD, both MDRD and CKD-EPI show that 64 percent have hypertension, more than one-third are unaware of their condition, 14 percent are not treated, and 11 percent are on a successful treatment regime.

With both MDRD and CKD-EPI, 80 percent of participants with Stage 3–4 CKD have hypercholesterolemia (based on elevated LDL), but only 18–22 percent are treated and brought to levels recommended by clinical practice guidelines. In those with less severe CKD, 48–49 percent have hypercholesterolemia, while less than one-third are aware of their condition and adequately controlled. Approximately 20 percent of CKD patients have high (240+) total cholesterol levels and HDL cholesterol below the recommended levels, while 63 percent of participants with Stage 1–2 CKD and 47 percent of those with Stage 3–4 CKD have glycohemoglobin levels above the recommended 7 percent guideline. ✣ **TABLE 1.E;** see page 166 for analytical methods. *NHANES 1999–2006 participants age 20 & older; those with Stage 5 CKD excluded.*

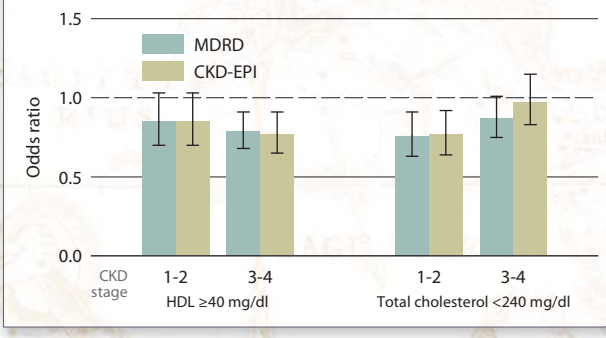
10*i* **Odds of awareness, treatment, & control of hypertension, by CKD stage & method used to estimate GFR**



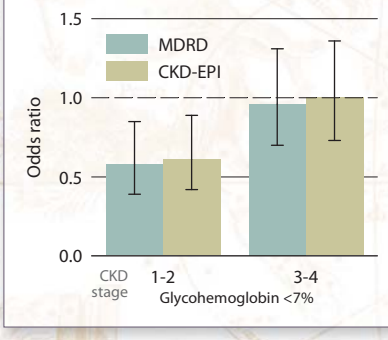
11*i* **Odds of awareness, treatment, & control of hypercholesterolemia, by CKD stage & method used to estimate GFR**



12*i* **Odds of meeting target HDL & total cholesterol levels, by CKD stage & method used to estimate GFR**



13*i* **Odds of diabetes control, by CKD stage & method used to estimate GFR**

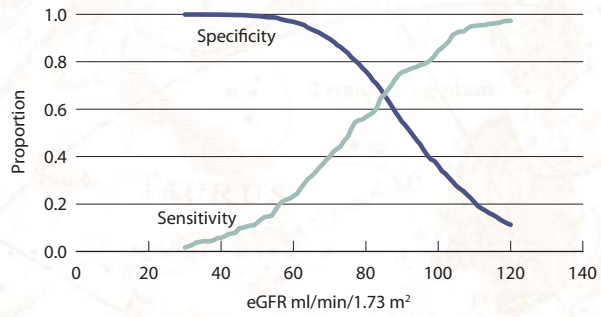


Regardless of the method used to estimate GFR, participants with CKD are 4–5 times more likely to have hypertension than those without. Patients with Stage 1–2 CKD are more likely to be aware of their condition and on a successful treatment protocol compared to those with Stage 3–4 CKD. And those with Stage 1–2 CKD are also nearly twice as likely to receive anti-hypertensive medications in the form of an ACE inhibitor, angiotensin receptor blocker, or renin inhibitor than those with more advanced CKD.

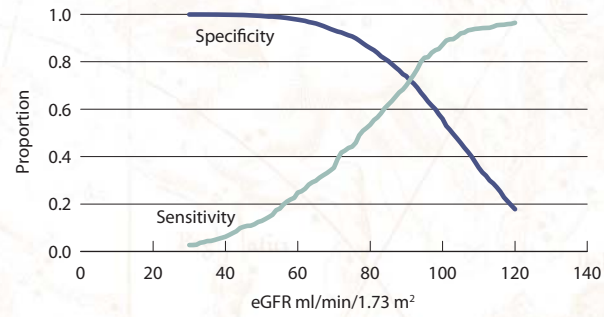
With the MDRD equation, the likelihood of hypercholesterolemia is more than four times greater in participants with Stage 3–4 CKD than in those with no CKD, and it is three times greater with CKD-EPI. Both methods show that participants with Stage 3–4 CKD are more likely to be aware of and suitably treated for their condition than those with less severe CKD, but the likelihood of receiving a lipid lowering medication is similar for all CKD stages.

With both methods, the odds of meeting a high density lipid (HDL) level of 40 mg/dl or higher are greater in participants with Stage 3–4 CKD than in those with less severe CKD; the opposite is true for total cholesterol levels. Participants with Stage 1–2 CKD are more likely to have a total cholesterol of less than 240 mg/dl than those with CKD of Stages 3–4. And with both eGFR methods, diabetes control is nearly twice as likely in participants with less severe CKD. ⁜ **Figures 1.10–13;** see page 166 for analytical methods. *NHANES 1999–2006 participants age 20 & older; those with Stage 5 CKD excluded. For Figures 1.10–1.11, *participants with hypertension; **participants with hypercholesterolemia.*

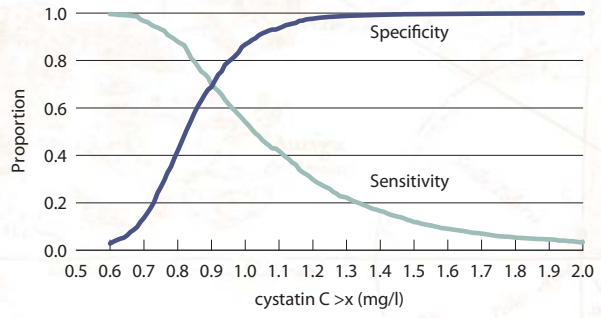
1.14i Predicting death: sensitivity & specificity of different eGFR thresholds: MDRD equation



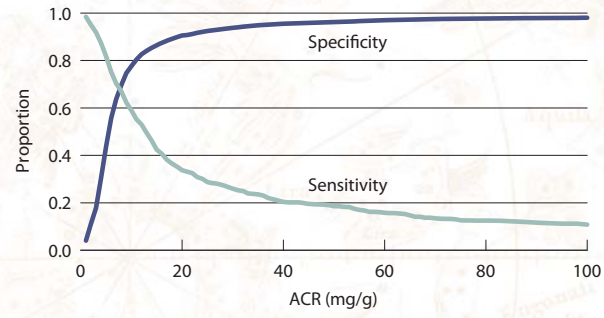
1.15i Predicting death: sensitivity & specificity of different eGFR thresholds: CKD-EPI equation



1.16i Predicting death: sensitivity & specificity of different cystatin C thresholds



1.17i Predicting death: sensitivity & specificity of different ACR thresholds



For screening purpose, it can be useful to know the efficacy of different threshold levels for predicting death or survival. For death within a finite time interval, a threshold where individuals classified as "normal" show low mortality rates (a high proportion of true negatives, high specificity for predicting death) and those classified as "abnormal" show high mortality rates (a high proportion of true positives, high sensitivity for predicting death) might be attractive for defining subgroups in which intensive follow-up and treatment may be appropriate, as well as for classification purposes.

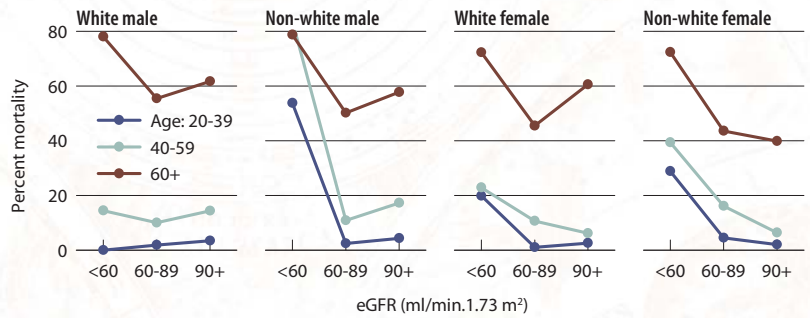
Figures here show the sensitivity and specificity, for predicting death, of different threshold levels of commonly-used renal function measures among representative U.S. adults between 1988 and 1994, followed through 2006. Considered as continuous variables, the C-statistic for death (an index of discrimination between survival and death with perfection denoted by a value of 1) was 0.81 with the CKD-EPI equation, 0.79 with serum cystatin C, 0.75 with the MDRD equation, and 0.69 with ACR. For eGFR and ACR, respective thresholds of 60 ml/min/1.73 m² and 30 mg/g are highly specific but highly insensitive, as the vast majority of subjects who died during the observation period had an eGFR greater than 60 and an ACR less than 30. Recognizing that gains in sensitivity are always accompanied by losses in specificity, and vice versa, thresholds of maximizing sensitivity plus specificity are approximately 90 ml/min/1.73 m² for eGFR, and 10 mg/g for ACR. For cystatin C, the threshold value showing the highest maximum combined value of sensitivity and specificity for predicting death is approximately 0.9 mg/l. ✣ **Figure 1.14–17;** see page 166 for analytical methods. *NHANES III (1988–1994) participants age 20 & older.*

Specificity/sensitivity

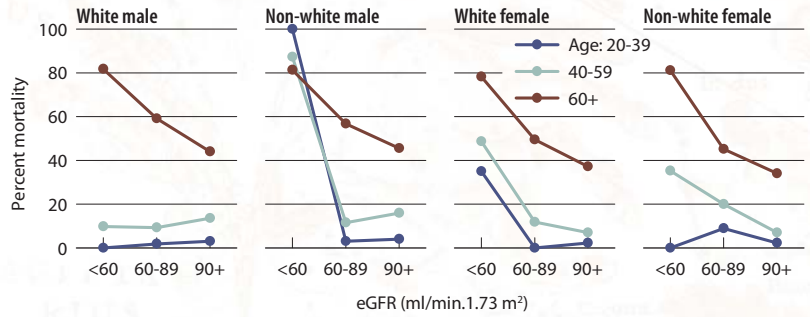
eGFR at threshold x
- "sensitivity"= (eGFR ≤x | died)
- "specificity"= (eGFR >x | survived)

ACR at threshold X
- "sensitivity"= (ACR >x | died)
- "specificity"= (ACR ≤xW | survived)

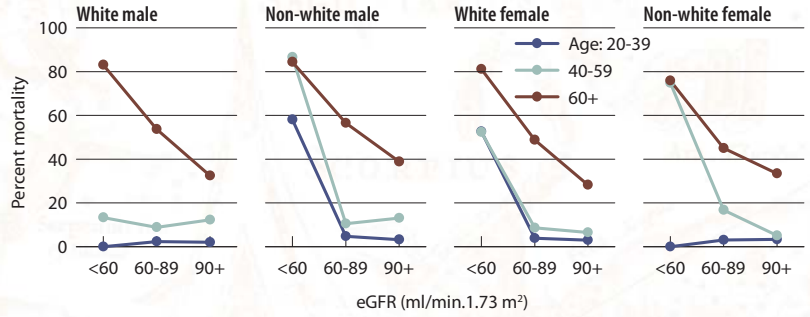
I18i **Mortality rates in NHANES 1988–1994 participants, by age, gender, race, & eGFR: MDRD equation**



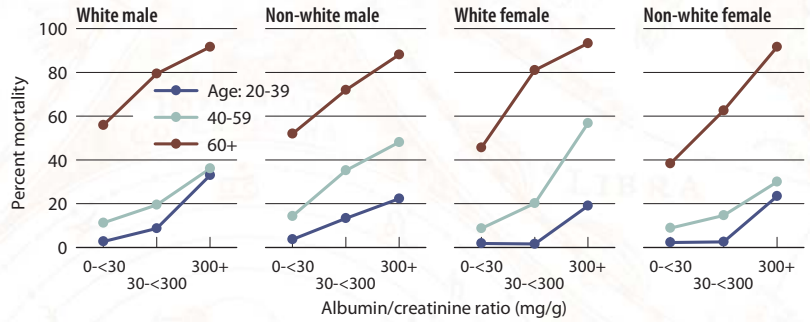
I19i **Mortality rates in NHANES 1988–1994 participants, by age, gender, race, & eGFR: CKD-EPI equation**



I20i **Mortality rates in NHANES 1988–1994 participants, by age, gender, race, & eGFR: cystatin C**



I21i **Mortality rates in NHANES 1988–1994 participants, by age, gender, race, & albumin/creatinine ratio**



Here we show proportions of NHANES 1988–1994 participants who died during a follow-up interval extending to December 31, 2006, and categorize them by interactions of race, gender, and renal function. In general, because of low mortality rates, caution must be used when interpreting mortality in subgroups younger than 40.

Restricting comparisons to participants age 40 or older, and using the MDRD equation to estimate GFR, the expected monotonic association between lower eGFR category and higher mortality is present only for white females age 40–59 and non-white females age 40 and older; for all other categories, mortality is highest with an eGFR less than 60 ml/min/1.73 m², lowest with an eGFR 60–89, and intermediate with an eGFR of 90 or above.

Similarly restricting comparisons to those age 40 or greater and using the CKD-EPI equation to estimate GFR, the expected monotonic association between lower eGFR and higher mortality is absent in males age 40–59 (with higher mortality in the subgroup with an eGFR of 90 or greater than among those with an eGFR of 60–89).

Using a similar strategy with the cystatin C-based eGFR, the expected monotonic association pattern is present in each subgroup except white and non-white males age 40–59.

When spot urinary albumin/creatinine ratio (ACR) is categorized as less than 30, 30–299, and 300 mg/g or more, and comparisons are restricted to those age 40 or older, the expected monotonic association between rising ACR and rising mortality is present in each of the subgroups studied. ✣ **FIGURES I.18–21;** see page 166 for analytical methods. *NHANES III (1988–1994) participants age 20 & older, followed to December 31, 2006.*

In general, screening strategies show greater sensitivity for detecting eGFRs less than 60 ml/min/1.73 m^2 with the CKD-EPI equation than with the MDRD or cystatin C equations. **TABLE I.B**

In cumulative frequency distributions of eGFR in U.S. adults, CKD-EPI and cystatin C methodologies for eGFR calculation yield higher GFR estimates than those achieved with the MDRD method. **FIGURES I.2–4**

Diabetes, hypertension, and cardiovascular disease are much more common in persons with CKD than in those without, and there is a trend towards higher prevalence estimates with rising CKD stage. **TABLE I.C**

With the MDRD method used to estimate GFR, 80.5 percent of participants with CKD of Stages 3–4 have hypertension; only 20 percent, however, are aware of their condition and on a successful treatment regime. Using the CKD-EPI method, 84.4 percent of Stage 3–4 participants have hypertension, and 19.5 percent are aware of their condition and receiving adequate treatment. **TABLE I.E**

Regardless of the method used to estimate GFR, NHANES participants with CKD are 4–5 times more likely to have hypertension than those without. **FIGURE I.10**