

# chapter one

## CHRONIC KIDNEY DISEASE IN THE GENERAL POPULATION

I hear the human race  
Is fallin' on its face  
And hasn't very far to go,  
But ev'ry whippoorwill  
Is sellin' me a bill,  
And tellin' me it just ain't so.

RICHARD RODGERS & OSCAR HAMMERSTEIN II,  
"A COCKEYED OPTIMIST"

40	strategies for identifying CKD   comorbidity
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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 of clear public health relevance — and compare prevalence estimates in 2001–2004 and 2005–2008. While the prevalence of diabetes has clearly increased, and the prevalence of congestive heart failure has remained stable, the prevalence of CKD appears to have declined slightly, from 15.8 percent to 15.1 percent when calculated with the MDRD formula, and from 14.7 percent to 14.5 percent when calculated with the CKD-EPI formula; prevalence estimates of CKD in 1988–1994 were 12.8 and 12 percent, respectively.

Estimates of CKD burden are partly dependent on the equation used to define the estimated glomerular filtration rate (eGFR): when the newer CKD-EPI equation is used, the prevalence of eGFR less than 60 ml/min/1.73 m<sup>2</sup> is low-

ered by a factor of 0.88 (6.9 percent versus 7.8 percent) compared with the estimate from the older MDRD Study equation. Regardless of the method used to estimate GFR, low eGFR and high urinary albumin/creatinine ratio (ACR) are most likely to be found in the presence of age greater than 60, diabetes, hypertension, and cardiovascular disease.

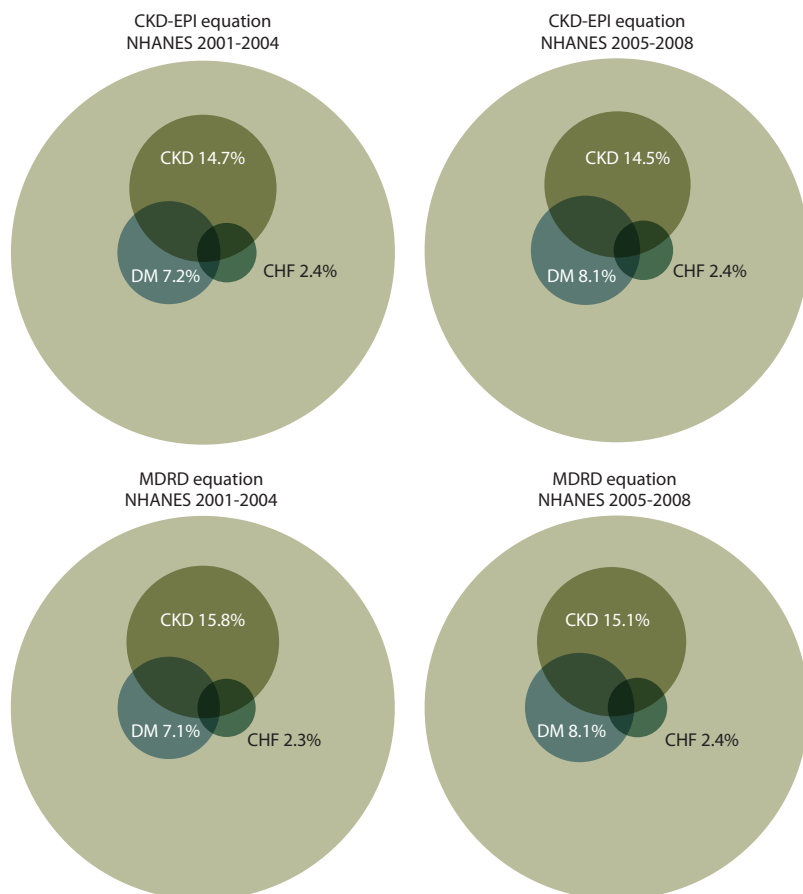
Exploring the implications of CKD, diabetes, and cardiovascular disease in the general population, this chapter sets the stage for Chapter Two, in which we discuss the implications of CKD in datasets that are less well defined in terms of biochemical data, but that provide extensive information on morbidity,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

>> **Figure 1.1:** see page 122 for analytical methods. *NHANES participants age 20 & older.*



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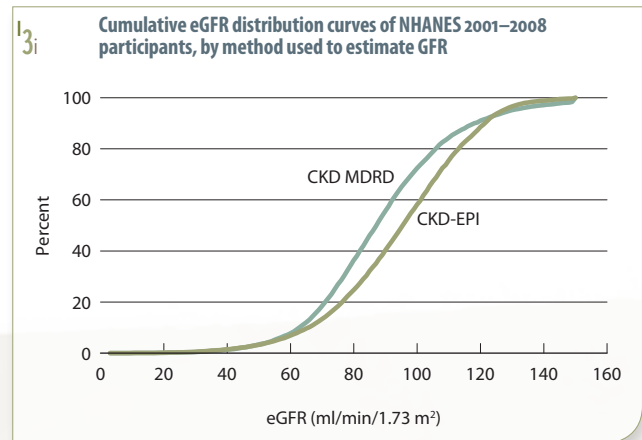
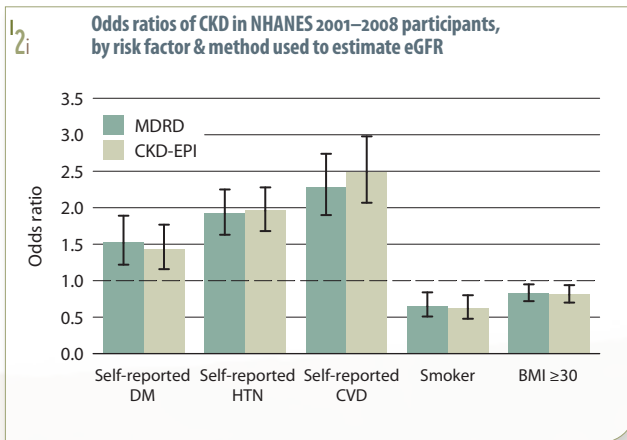
**Distribution of NHANES participants with diabetes, congestive heart failure, & markers of CKD, with GFR estimated by MDRD & CKD-EPI equations**



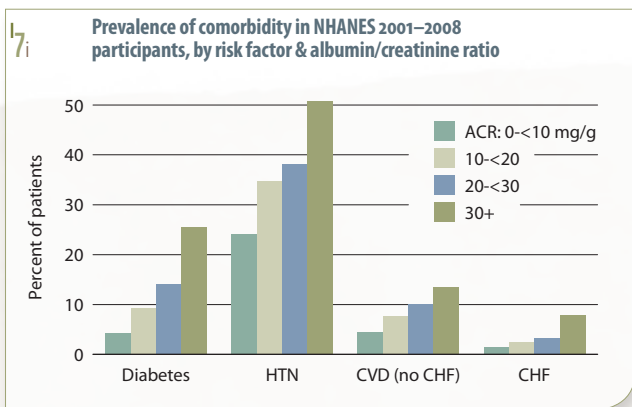
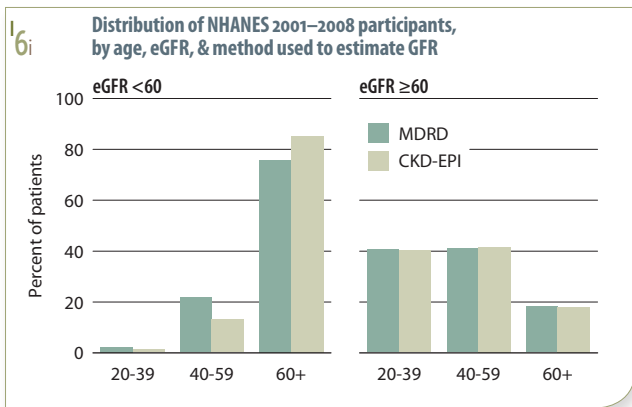
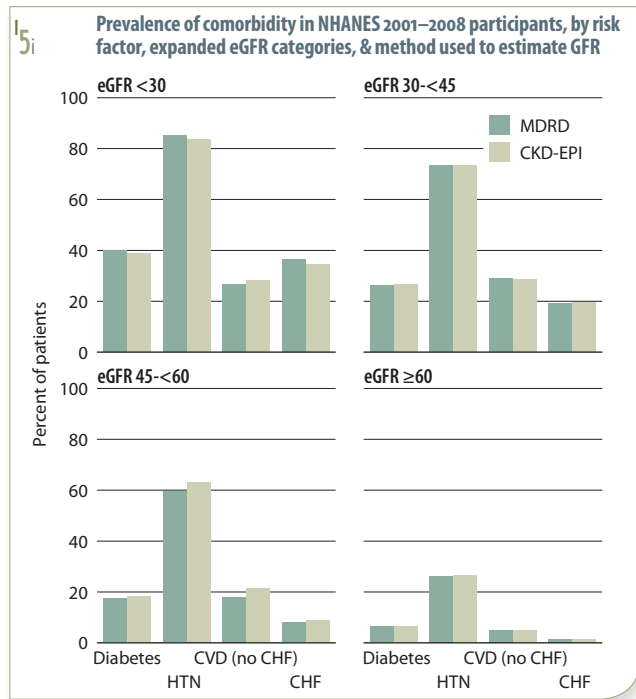
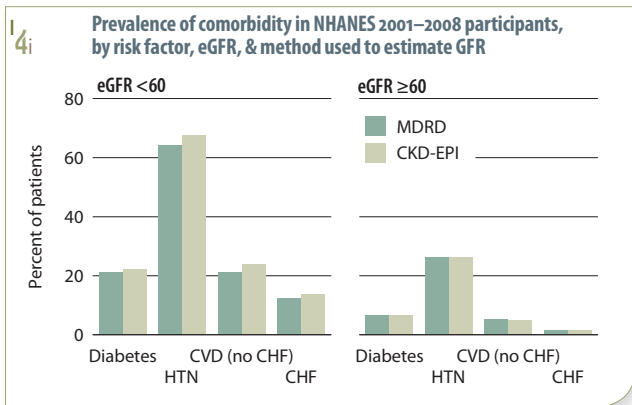
With a single creatinine-based eGFR and the MDRD and CKD-EPI equations, 26 percent of NHANES participants age 60 or older have an eGFR of less than 60 ml/min/1.73 m<sup>2</sup> (CKD Stages 3–5); 19.7 percent have a urinary albumin/creatinine ratio greater or equal to 30 mg/g. For all adults, multivariate associations of CKD for eGFR and ACR methodologies include older age, female gender, and self-reported diabetes, hypertension, and cardiovascular disease. >> **Table 1.a & Figure 1.2**; see page 122 for analytical methods. *NHANES 2001–2008 participants age 20 & older. For Figure 1.2, odds ratios use populations without the risk factor as reference.*

**1.a** Prevalence & odds ratios of CKD in NHANES 2001–2008 participants, by ACR & method used to estimate GFR, age, gender, race/ethnicity, & risk factor (percent of participants)

	eGFR: MDRD		eGFR: CKD-EPI		Albumin/creatinine ratio	
	eGFR <60 ml/min/1.73 m <sup>2</sup>	Odds ratio	eGFR <60 ml/min/1.73 m <sup>2</sup>	Odds ratio	ACR ≥30 mg/g	Odds ratio
20-39	0.5	ref.	0.2	ref.	5.7	ref.
40-59	4.3	6.8	2.3	7.0	8.5	1.2
60+	26.0	33.0	26.0	63.9	19.7	2.5
Male	6.2	ref.	5.7	ref.	9.2	ref.
Female	9.3	1.6	8.1	1.4	10.6	1.2
Non-Hispanic white	9.2	ref.	8.1	ref.	9.1	ref.
Non-Hispanic Af Am	5.4	0.6	5.7	0.9	13.1	1.5
Other	3.2	0.5	2.6	0.5	11.4	1.7
Self-reported diabetes	21.3	1.5	19.8	1.4	33.4	3.4
Self-reported hypertension	17.2	1.9	16.0	2.0	17.3	1.6
Self-reported CVD	30.1	2.3	29.8	2.5	24.8	1.7
Current smoker	3.5	0.7	2.7	0.6	9.8	1.4
Obese (BMI ≥30)	8.1	0.8	7.1	0.8	12.4	1.2
All	7.8		6.9		9.9	



In cumulative frequency distributions of eGFR in U.S. adults, the creatinine-based CKD-EPI methodology for eGFR calculations yields higher estimates of GFR than those achieved with the creatinine-based MDRD method. >> **Figure 1.3**; see page 122 for analytical methods. *NHANES 2001–2008 participants age 20 & older.*



### CKD STAGE MARKERS

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

With both creatinine-based MDRD and CKD-EPI estimates, prevalence estimates of diabetes, hypertension, cardiovascular disease (CVD, not including CHF), and CHF are noticeably higher in participants with eGFRs below 60 ml/min/1.73 m<sup>2</sup>. Approximately 64–68 percent of NHANES participants with an eGFR less than 60, for example, have hypertension, compared to 26 percent of those with an eGFR of 60 or greater, and their prevalence of CVD is nearly five-fold greater.

The prevalence of disease rises with CKD severity. In participants with eGFRs less than 30, 30–45, and 45–60, for example, 40, 27, and 18 percent have diabetes, compared to 7 percent of those with an eGFR of 60 or above. And in participants with an eGFR less than 30, 84–85 percent have hypertension and 35–36 percent have CHF, compared to 5.0 and 1.5 percent, respectively, of participants with an eGFR of 60 or greater.

Slightly more than 75 percent of NHANES participants with an MDRD-estimated eGFR less than 60 ml/min/1.73 m<sup>2</sup> are age 60 years or older, compared with 85 percent when eGFR is calculated with the CKD-EPI equation.

The prevalence of comorbid illness among NHANES participants rises with albumin/creatinine ratio (ACR). Four percent of participants with an ACR less than 10 mg/g have diabetes, compared to 26 percent of those whose ACR is 30 or greater. Hypertension and CVD are present in 24 and 4.5 percent of participants with an ACR below 10, compared to 51 and 13.5 percent of those with an ACR of 30 or greater. >> Figures 1.4–7; see page 122 for analytical methods. *NHANES 2001–2008 participants age 20 & older.*

**Table 1.b: Awareness, treatment, & control of hypertension, hypercholesterolemia, HDL, total cholesterol, & diabetes, by ACR, eGFR, & method used to estimate GFR (percent of NHANES participants)**

	1999–2004 eGFR: MDRD (ml/min/1.73 m <sup>2</sup> )		eGFR: CKD-EPI (ml/min/1.73 m <sup>2</sup> )		ACR (mg/g)		2005–2008 eGFR: MDRD (ml/min/1.73 m <sup>2</sup> )		eGFR: CKD-EPI (ml/min/1.73 m <sup>2</sup> )		ACR (mg/g)	
	<60	≥60	<60	≥60	30+	<30	<60	≥60	<60	≥60	30+	<30
<b>Hypertension, by current hypertensive status<sup>1</sup></b>												
Non-hypertensive status	19.0	71.9	14.9	71.5	30.1	71.7	19.6	70.6	15.0	70.0	30.8	70.7
Hypertensive (measured/treated)	81.0	28.1	85.1	28.6	70.0	28.3	80.4	29.4	85.0	30.0	69.2	29.4
<b>Control of hypertension among hypertensive patients<sup>2</sup></b>												
Unaware	39.5	76.5	35.4	76.2	54.1	75.8	34.0	72.9	29.1	72.6	46.3	72.5
Aware, not treated	7.1	8.7	7.2	8.7	9.4	8.5	5.6	8.8	6.1	8.7	10.9	8.3
Aware, treated, uncontrolled	38.3	7.4	42.3	7.6	29.8	7.7	39.1	7.0	41.6	7.3	31.1	7.2
Aware, treated, controlled	15.1	7.4	15.1	7.6	6.7	8.1	21.3	11.4	23.3	11.5	11.6	12.0
<b>Hypercholesterolemia (LDL): LDL cholesterol<sup>3</sup></b>												
Within ATP-III target LDL range	18.8	64.5	19.2	64.0	44.9	62.5	31.2	78.4	34.2	77.5	68.7	75.9
Hypercholesterolemic (measured or treated)	81.2	35.5	80.8	36.0	55.1	37.5	68.8	21.6	65.9	22.6	31.3	24.1
<b>Control of hypercholesterolemia (LDL) among participants with hypercholesterolemia (LDL)<sup>4</sup></b>												
Unaware	50.7	71.0	49.8	70.9	56.3	70.5	49.4	71.7	51.6	71.0	67.0	70.4
Aware, not treated	8.2	7.9	6.2	8.0	10.1	7.9	9.3	6.6	6.8	6.8	3.7	7.1
Aware, treated, uncontrolled	23.0	8.0	22.9	8.2	16.3	8.6	22.4	5.7	18.2	6.3	10.3	6.6
Aware, treated, controlled	18.1	13.1	21.1	12.9	17.3	13.0	18.9	16.1	23.5	15.8	19.1	15.8
<b>HDL cholesterol in ATP III target range<sup>5</sup></b>												
HDL <40 mg/dl (ATP III target)	14.4	16.0	14.0	16.0	18.7	15.5	15.0	15.5	15.0	15.5	18.8	15.1
HDL 40 mg/dl or higher (at/above ATP III target)	85.6	84.0	86.0	84.0	81.3	84.5	85.0	84.5	85.1	84.5	81.3	84.9
<b>Total cholesterol<sup>6</sup></b>												
<200 (desirable)	51.8	54.0	53.8	53.8	55.9	53.8	58.9	56.2	61.8	56.1	58.3	56.1
200–239 (borderline high)	33.1	31.2	30.8	31.4	23.4	32.1	26.0	29.5	23.8	29.5	24.8	29.8
240+ (high)	15.1	14.8	15.4	14.8	20.7	14.1	15.1	14.3	14.4	14.4	17.0	14.1
<b>Control of diabetes among diabetic patients<sup>7</sup></b>												
Glycohemoglobin <7% (controlled)	54.8	46.8	54.8	47.0	39.1	53.0	56.9	54.6	58.4	54.3	46.7	59.5
Glycohemoglobin 7% or higher (uncontrolled)	45.2	53.2	45.2	53.0	60.9	47.0	43.1	45.4	41.6	45.7	53.3	40.5

Here we use NHANES data from two time periods to evaluate awareness, treatment, and control of disease conditions, using estimates of glomerular filtration rate (eGFR) from the MDRD and CKD-EPI methods (both creatinine-based).

In 1999–2004, using the MDRD method, 81 percent of participants with an eGFR less than 60 ml/min/1.73 m<sup>2</sup> had hypertension; only 15 percent, however, were aware of their condition and on a successful treatment regime. In 2005–2008 participants, 80 percent were hypertensive and 21 percent were being treated successfully. With the CKD-EPI method, 85 percent of the 1999–2004 cohort were hypertensive and 15 percent were being treated successfully, compared to 85 and 23 percent in 2005–2008. Among 1999–2004 participants with eGFRs of 60 or greater (both MDRD and CKD-EPI formulas), 28 percent

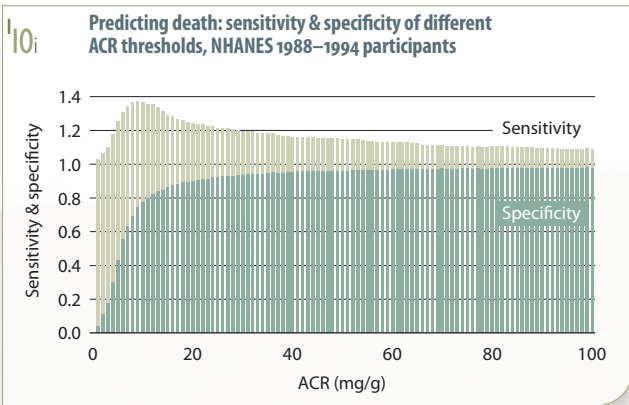
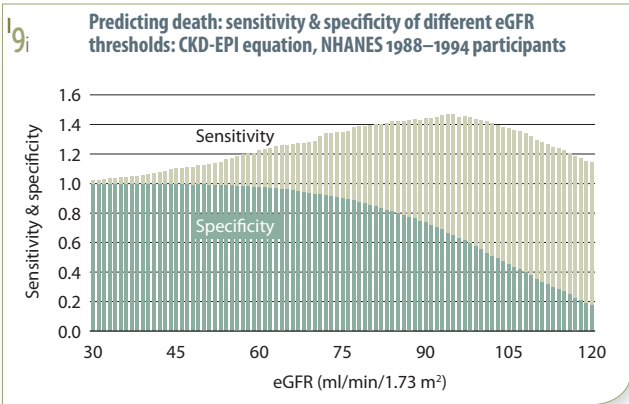
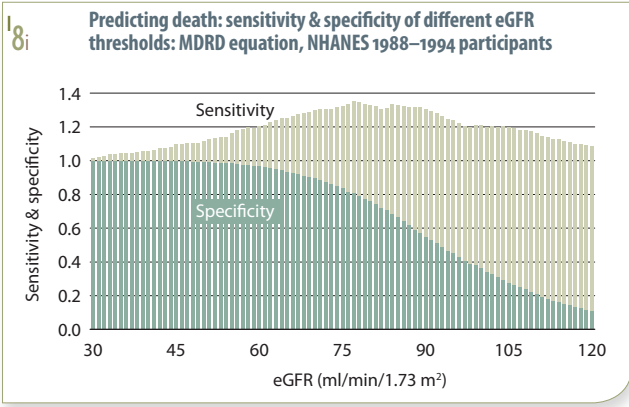
had hypertension and approximately 7 percent were being successfully treated compared to 30 and 11 percent in 2005–2008.

With both the MDRD and CKD-EPI formulas, 81 percent of 1999–2004 participants with eGFRs less than 60 had hypercholesterolemia (based on elevated LDL), but only 18–21 percent were successfully treated. The proportion of participants with hypercholesterolemia in the later period was lower, at 66–69 percent, but little improvement was observed in rates of successful treatment.

In 2005–2008, approximately 15 percent of participants with CKD had a high total cholesterol level, while 40–50 percent had glycohemoglobin levels above the recommended 7 percent. >> **Table 1.b**; see page 123 for analytical methods. *NHANES 1999–2008 participants age 20 & older; those with Stage 5 CKD excluded.*

## ANALYSIS DEFINITIONS

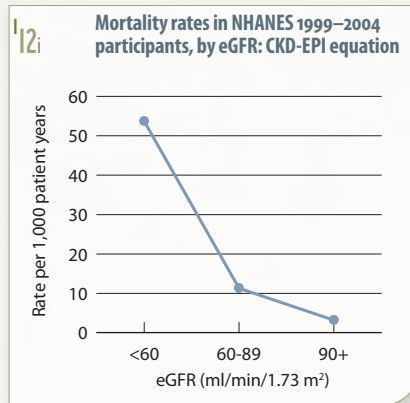
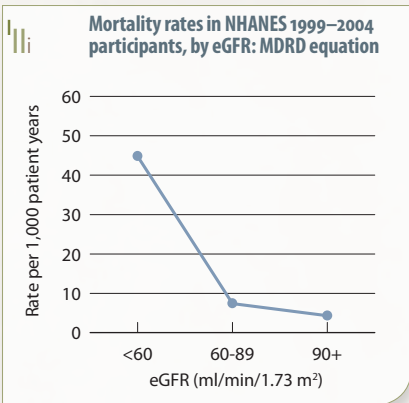
- 1 Hypertension defined as blood pressure ≥130/≥80 for those with CKD and diabetes; otherwise ≥140/≥90, or self-reported treatment for hypertension.
- 2 Awareness and treatment are self-reported. Control defined as <130/<80 for those with CKD and diabetes; otherwise <140/<90.
- 3 Hypercholesterolemia 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.



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

Figures 1.8–10 show sensitivity and specificity values for different threshold renal values among NHANES III participants (1988–1994) followed through 2006. Conventionally used thresholds — like  $<60$  ml/min/1.73 m<sup>2</sup> for eGFR and  $\geq 30$  mg/g for ACR — exhibit low sensitivity and high specificity values for predicting death. >> Figures 1.8–10; see page 123 for analytical methods. *NHANES III (1988–1994) participants age 20 & older.*

Here we show annual mortality rates in 1994–2004 NHANES participants. For eGFR below 90 ml/min/1.73 m<sup>2</sup>, mortality rates are higher with the CKD-EPI formula; for eGFRs above 90, rates are lower. >> Figures 1.11–12; see page 123 for analytical methods. *NHANES 1999–2004 participants age 20 & older.*



**SPECIFICITY/SENSITIVITY**

eGFR at threshold x  
 “sensitivity” = (eGFR  $\leq$  x | died)  
 “specificity” = (eGFR  $>$  x | survived)

ACR at threshold X  
 “sensitivity” = (ACR  $>$  x | died)  
 “specificity” = (ACR  $\leq$  x | survived)

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## odds of CKD in NHANES PARTICIPANTS with EGFR <60 ml/min/1.73 m<sup>2</sup> OR ACR ≥30 mg/g

SELF-REPORTED (SR) RISK FACTORS

MDRD EQUATION	» SR DIABETES 21% » SR HYPERTENSION 17% » SR CARDIOVASCULAR DISEASE 30% (TABLE I.A)
CKD-EPI EQUATION	» SR DIABETES 20% » SR HYPERTENSION 16% » SR CARDIOVASCULAR DISEASE 30% (TABLE I.A)
ACR	» SR DIABETES 33% » SR HYPERTENSION 17% » SR CARDIOVASCULAR DISEASE 25% (TABLE I.A)

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## Prevalence of comorbidity in NHANES 2001–2008 PARTICIPANTS

EGFR <60 (MDRD EQUATION)	» DIABETES 21% » HYPERTENSION 64% » CVD 21% » CHF 12% (FIG I.4)
EGFR <60 (CKD-EPI EQUATION)	» DIABETES 22% » HYPERTENSION » 68% » CVD 24% » CHF 14% (FIG I.4)
EGFR ≥60 (MDRD AND CKD-EPI EQUATIONS)	» DIABETES 7% » HYPERTENSION 26% » CVD 5% » CHF 2% (FIG I.4)

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## mortality rates in NHANES 1999–2004 PARTICIPANTS

DEATHS PER 1,000 PATIENT YEARS

MDRD AND CKD-EPI EQUATIONS	» EGFR <60 45 » EGFR 60–89 7 » EGFR 90+ 4 (FIG I.II)
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