

# The Incidence of End-Stage Renal Disease Is Increasing Faster than the Prevalence of Chronic Renal Insufficiency

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**Background:** The steady increase in end-stage renal disease (ESRD) incidence is a worldwide public health crisis.

**Objective:** To determine whether the increasing incidence of ESRD in the United States is preceded by increased prevalence of chronic renal insufficiency.

**Design:** Birth cohort analysis.

**Setting:** Nationally representative Second and Third National Health and Nutrition Examination Surveys (NHANES II [1976–1980] and III [1988–1994]) and nationally comprehensive U.S. Renal Data System registry.

**Patients:** Adults, 20 to 74 years of age, surveyed in NHANES II (midpoint, 1978) and NHANES III (midpoint, 1991), and adults, 25 to 79 years of age, who developed ESRD in 1983 and 1996.

**Measurements:** Prevalent chronic renal insufficiency (estimated glomerular filtration rate, 15 to 59 mL/min per 1.73 m<sup>2</sup>) and new ESRD cases.

**Results:** From 1978 to 1991, the number of adults age 20 to 74 years with chronic renal insufficiency increased from 2.6 to 3.9

million, an increase in prevalence from 1970 to 2460 per 100 000 persons. However, the increased incidence of ESRD was even greater during this period. For every 1000 adults with chronic renal insufficiency in 1978, 9 new cases of ESRD developed in 1983, but every 1000 adults with chronic renal insufficiency in 1991 produced 16 new cases of ESRD in 1996 (relative risk, 1.7 [95% CI, 1.1 to 2.7]).

**Limitations:** We could not follow individual patients with chronic renal insufficiency for the development of ESRD, and we used estimated rather than measured glomerular filtration rate.

**Conclusions:** During the period examined, growth in incident ESRD outpaced growth in prevalent chronic renal insufficiency, demonstrating that the ESRD epidemic in the United States is not merely a function of more cases of kidney disease. Future research should examine other potential contributors to ESRD growth, such as improved survival from nonrenal diseases and more liberal entry into treatment programs.

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The steady increase in the incidence of treated end-stage renal disease (ESRD) and its associated morbidity and mortality is an urgent worldwide public health problem. The number of new cases of ESRD in the United States is projected to be 650 000 by 2010, with accompanying Medicare expenditures of \$28 billion (1). A major goal of Healthy People 2010 is to reduce the incidence of ESRD (2). A crucial first step for devising preventive strategies and planning future health care needs is to better understand the driving forces behind ESRD growth.

In 1992, Port (3) enumerated 3 factors that may explain the observed increase in treated ESRD: broader acceptance of patients into ESRD therapy, improved prevention or outcomes from cardiovascular disease and other conditions resulting in more patients surviving to ESRD, and a true increase in renal disease prevalence. Postulated explanations for increasing renal disease include a greater proliferation of environmental toxins (3); increased use of nephrotoxic agents, such as analgesic medications (4); and the growing epidemic of diabetes mellitus. Although ESRD incidence continues to increase, we still do not know the relative contributions of these 3 important factors.

For this study, we hypothesized that actual growth in kidney disease is only a minor contribution to the ongoing ESRD epidemic in the United States. We tested this hypothesis by examining the change in population prevalence of kidney disease over 13 years relative to parallel changes

in the incidence of ESRD. We further estimated the proportional contributions of growth in the U.S. population and in chronic renal insufficiency prevalence to the increasing numbers of new ESRD cases during the study period.

## METHODS

### Data Sources and Patients Studied

Our analyses used data from the nationally representative Second and Third National Health and Nutrition Examination Surveys (NHANES II and III) and the comprehensive U.S. Renal Data System (USRDS) registry. The National Center for Health Statistics conducted NHANES II (1976–1980) (5) and III (1988–1994) (6) to provide data on the health and nutritional status of the noninstitutionalized U.S. population. The USRDS is a nationally comprehensive registry of ESRD treatment in the United States (2). Our analyses took advantage of the fact that both NHANES and USRDS apply to the entire U.S. population of black and white adults.

### Definition of Chronic Renal Insufficiency

Chronic renal insufficiency was defined as a glomerular filtration rate (GFR) of 15 to 59 mL/min per 1.73 m<sup>2</sup>, corresponding to chronic kidney disease stages 3 and 4 of the recently proposed National Kidney Foundation classification (7). Glomerular filtration rate was estimated by using the simplified Modification of Diet in Renal Disease (MDRD) study equation (8, 9):

**Context**

The causes of the rapid growth in incidence of end-stage renal disease (ESRD) are unknown but may include an increase in prevalence of renal disease; more liberal acceptance into ESRD therapy; or improved survival from competing causes of death, such as cardiovascular disease.

**Contribution**

Comparison of data from the Second and Third National Health and Nutrition Examination Surveys and the U.S. Renal Data System shows that the increase in ESRD cannot be explained by increasing prevalence of chronic renal insufficiency.

**Implications**

Interventions aimed at the primary and secondary prevention of kidney disease alone are unlikely to reduce the increase in incidence of ESRD.

—The Editors

$\text{GFR (mL/min per } 1.73 \text{ m}^2) = 186 \times (\text{serum creatinine level [mg/dL]})^{-1.154} \times (\text{age})^{-0.203} \times [0.742, \text{ if female}] \times [1.212, \text{ if black}]$

To correct for calibration differences in creatinine level measurements between MDRD and NHANES, we subtracted 0.23 mg/dL (20.4  $\mu\text{mol/L}$ ) from all creatinine values in NHANES (10). We did not find any calibration differences between creatinine values in NHANES II and III. Specifically, the mean and median serum creatinine levels for white persons age 20 to 39 years without diabetes or hypertension in both NHANES II and III were 1.1 mg/dL (97.3  $\mu\text{mol/L}$ ) in men and 0.9 mg/dL (79.6  $\mu\text{mol/L}$ ) in women.

Although serum creatinine level was to be measured in 14 479 NHANES II examinees age 12 to 74 years, data were missing for 28% (4018 examinees). The 2 most important reasons for these missing data were loss of specimen in shipping (13%) and low priority in cases of inadequate sera (11%) (creatinine was ranked 17 out of 18 assays). Among the 10 461 NHANES II examinees with measured creatinine levels, 8305 were 20 to 74 years of age and were classified as black or white by self-report. These 8305 individuals form the basis of our chronic renal insufficiency population estimation in 1978 (midpoint of NHANES II).

In NHANES III, serum creatinine level was to be measured in 20 216 examinees age 12 years and older, but data were missing for 7% (1494 examinees). Among the 18 722 NHANES III examinees with measured creatinine levels, 13 350 were 20 to 74 years of age and were classified as black or white by self-report. These 13 350 individuals form the basis of our chronic renal insufficiency population estimation in 1991 (midpoint of NHANES III).

We limited our analyses of chronic renal insufficiency

prevalence to adults who were 20 to 74 years of age because NHANES II did not include adults older than 74 years. We also limited our analysis to persons classified as white or black to ensure compatible race classification across data sets.

**Ascertainment of New ESRD Cases**

Persons were defined as having ESRD if they received treatment with either dialysis or transplantation. Our birth cohort analysis assumed that adults age 25 to 79 years who developed ESRD in 1983 came from the source population with chronic renal insufficiency age 20 to 74 years in the United States sampled in NHANES II (midpoint, 1978). Similarly, adults age 25 to 79 years who developed ESRD in 1996 came from the source population with chronic renal insufficiency age 20 to 74 years in the United States sampled in NHANES III (midpoint, 1991). We chose the 5-year follow-up on the basis of the published rate of GFR loss among patients with chronic renal insufficiency, but we conducted sensitivity analyses that varied the follow-up interval from 3 to 8 years.

We conducted stratified analyses within these birth cohorts by age, sex, race, and diabetes status. Diabetes mellitus was defined in NHANES as self-report of physician-diagnosed diabetes mellitus (excluding gestational-only diabetes). Previous studies have shown that underascertainment was similar in NHANES II and III when self-report was compared with fasting glucose level (11, 12). The patients' nephrologists determined whether diabetes was the primary cause of ESRD when reported to USRDS.

**Statistical Analysis**

In estimating population variables, the complex survey sampling design of NHANES and probability weights were considered by using the *svy*means and *svy*tab functions in Stata software, version 7.0 (Stata Corp., College Station, Texas). We addressed the problem of missing creatinine values by using standard methods for adjusting sampling weights for nonresponse (13, 14). Specifically, we inflated the weights for respondents with creatinine levels in each strata defined by age, sex, and race, so that the sum of the inflated weights is equal to the sum of the original weights for that entire stratum. This reweighting procedure provides unbiased estimates of population variables, assuming that creatinine values were randomly missing in each demographic subgroup.

To estimate ESRD incidence among persons with chronic renal insufficiency, we computed the ratios of new ESRD cases reported in the USRDS for 1983 and 1996 divided by the population with chronic renal insufficiency estimated from NHANES II (midpoint, 1978) and NHANES III (midpoint, 1991), respectively. The increase in ESRD incidence in the population with chronic renal insufficiency was determined by dividing the ratio of the 1996 incidence by the 1983 incidence. The 95% CIs for this ratio accounted for variability in both the cases of chronic renal insufficiency (estimated by using standard

**Table 1. Estimated Prevalence of Chronic Renal Insufficiency among Adults Age 20 to 74 Years in 1978 and 1991 and Number of Newly Treated End-Stage Renal Disease Cases among Adults Age 25 to 79 Years in 1983 and 1996\***

Characteristic	Study	Total Sample (NHANES Participants), <i>n</i> ( <i>n</i> )†	Chronic Renal Insufficiency Cases (NHANES Participants), <i>n</i> ( <i>n</i> )†‡	Prevalence of Chronic Renal Insufficiency per Population of 100 000, <i>nt</i>	Incident ESRD Cases, <i>n</i> §
<b>Overall</b>	NHANES II (midpoint, 1978)	129 600 000 (8305)	2 560 000 (263)	1970	22 929 (in 1983)
	NHANES III (midpoint, 1991)	158 100 000 (13 350)	3 890 000 (397)	2460	60 323 (in 1996)
<b>Sex</b>					
Men	NHANES II	61 490 000 (3730)	1 160 000 (113)	1890	12 714
	NHANES III	76 220 000 (6245)	1 650 000 (184)	2160	32 556
Women	NHANES II	68 100 000 (4575)	1 390 000 (150)	2050	10 215
	NHANES III	81 830 000 (7105)	2 240 000 (213)	2740	27 767
<b>Diabetes</b>					
Yes	NHANES II	4 400 000 (353)	230 000 (31)	5300	5523
	NHANES III	7 090 000 (940)	721 000 (112)	10 200	27 146
No	NHANES II	125 200 000 (7952)	2 320 000 (232)	1860	17 406
	NHANES III	150 960 000 (12 410)	3 170 000 (285)	2100	33 174
<b>Race</b>					
White	NHANES II	116 700 000 (7414)	2 370 000 (232)	2030	15 518
	NHANES III	138 900 000 (9238)	3 500 000 (287)	2520	39 016
Black	NHANES II	12 900 000 (891)	190 000 (31)	1500	7411
	NHANES III	19 140 000 (4112)	394 000 (110)	2060	21 307
<b>Age</b>					
20–60 y	NHANES II	107 600 000 (5632)	840 000 (46)	780	14 808
	NHANES III	132 400 000 (10 393)	1 300 000 (97)	990	34 916
61–74 y	NHANES II	21 940 000 (2673)	1 720 000 (217)	7850	8121
	NHANES III	25 660 000 (2957)	2 580 000 (300)	10 100	25 407

\* ESRD = end-stage renal disease; NHANES II and III = Second and Third National Health and Nutrition Examination Survey (5, 6).

† Age 20 to 74 years.

‡ Chronic renal insufficiency is defined as a glomerular filtration rate (estimated by using the Modification of Diet in Renal Disease study formula [8, 9]) of 15 to 59 mL/min per 1.73 m<sup>2</sup>.

§ Age 25 to 79 years.

methods for NHANES) and the cases of ESRD (assumed to be Poisson-distributed). A Bonferroni correction for the 2 sources of variability was made (15).

### Additional Analyses Using a Modeling Approach

We conducted additional Poisson regression modeling to explore the contribution of temporal changes in the chronic renal insufficiency population to growth in ESRD incidence. In this analysis, new ESRD cases among persons 25 to 79 years of age in each year from 1985 to 1996 were tabulated and the incidence was determined in 8 demographic subgroups (cross-stratified by age, sex, and race). These subgroups were based on their population size in the U.S. Census 5 years before, defined by age (20 to 60 years or 61 to 74 years), sex, race (black or white), and year. For each of the 8 demographic subgroups, annual prevalence of chronic renal insufficiency from 1980 (first year after midpoint of NHANES II for which U.S. Census data on the demographic subgroup were available) to 1991 (midpoint of NHANES III) was estimated by linear interpolation from NHANES II to III.

We first determined the unadjusted rate of increase in newly treated ESRD cases among adults age 25 to 79 years from 1985 to 1996. Our second model adjusted for simple changes in population size and demographic composition. We then adjusted for changes in the prevalence of chronic

renal insufficiency (with the 5-year lag used in the birth cohort study) in our third model to investigate the extent to which increasing ESRD incidence could be attributed to increased chronic renal insufficiency prevalence. From the attenuation of the coefficient for calendar year across models, we inferred the degree to which these adjustments explained ESRD incidence over time. The effect of these multivariate adjustments on the temporal trend of ESRD growth was depicted graphically by superimposing the slopes of each model's regression line on a histogram showing the unadjusted incidence of ESRD.

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The funding source had no role in the collection, analysis, and interpretation of the data or in the decision to submit the manuscript for publication.

## RESULTS

### Birth Cohort Analysis

The overall number of black and white U.S. adults, 20 to 74 years of age, with chronic renal insufficiency increased from 2 560 000 persons to 3 890 000 persons from 1978 to 1991 (an increase in prevalence of 1970 to 2460 per 100 000 persons) (Table 1). From 1983 to 1996, the number of new cases of ESRD among black and white

**Table 2. Comparison of New End-Stage Renal Disease Cases per 1000 Persons with Prevalent Chronic Renal Insufficiency: National Health and Nutrition Examination Survey III versus National Health and Nutrition Examination Survey II\***

Patient Characteristic	ESRD Cases (1983) per 1000 Persons with Chronic Renal Insufficiency (1978) (NHANES II), <i>n</i>	ESRD Cases (1996) per 1000 Persons with Chronic Renal Insufficiency (1991) (NHANES III), <i>n</i>	Relative Risk for Progression to ESRD among Persons with Chronic Renal Insufficiency in 1991 (NHANES III) Compared with 1978 (NHANES II) (95% CI)
<b>Overall</b>	9	16	1.7 (1.1–2.7)
<b>Sex</b>			
Men	11	20	1.8 (1.0–3.3)
Women	7	12	1.7 (0.9–3.1)
<b>Diabetes</b>			
Yes	24	38	1.6 (0.7–3.5)
No	8	11	1.4 (0.9–2.2)
<b>Race</b>			
White	7	11	1.7 (1.1–2.7)
Black	39	54	1.4 (0.4–3.3)
<b>Age</b>			
20–60 y	18	27	1.5 (0.7–3.0)
61–74 y	5	10	2.1 (1.3–3.5)

\* ESRD = end-stage renal disease; NHANES II and III = Second and Third National Health and Nutrition Examination Survey (5, 6).

U.S. adults, 25 to 79 years of age, increased from 22 929 persons to 60 323 persons. This increase in ESRD incidence outpaced the increase in chronic renal insufficiency prevalence by 70% (calculated relative risk  $[(60\,323/3\,890\,000)/(22\,929/2\,560\,000)]$ , 1.7 [95% CI, 1.1 to 2.7]) (Table 2). We obtained the same results when we varied the time period between the ascertainment of chronic renal insufficiency prevalence and the incident ESRD cases from 3 to 8 years (relative risks, 1.7, 1.7, 1.7, 1.8, 1.8, and 1.8, respectively). Our results were also similar when we defined chronic renal insufficiency as body surface area–normalized, Cockcroft–Gault–estimated creatinine clearance of 15 to 59 mL/min per 1.73 m<sup>2</sup> (relative risk, 1.9 [CI, 1.2 to 2.9]) (16, 17). As shown in Table 2, the point estimates for the relative risks were similar across all strata examined. We found no significant interactions among the 4 subgroups tested—age, sex, race, and diabetes ( $P > 0.05$ ).

Since blood pressure control is recognized as a crucial intervention to slow the loss of GFR among patients with chronic renal insufficiency, we compared the mean blood pressure among patients with chronic renal insufficiency in NHANES II and III. Of interest, among patients with chronic renal insufficiency, blood pressure was actually higher in 1978 than in 1991 (145/87 mm Hg vs. 137/77 mm Hg;  $P < 0.05$ ). Nonetheless, patients with chronic renal insufficiency in 1991 were more likely to progress to treatment for ESRD.

### Risk in Subgroups

From 1978 to 1991, the prevalence of chronic renal insufficiency among adults with diabetes nearly doubled (from 5300 to 10 200 per 100 000 persons) (Table 1). In contrast, the prevalence of chronic renal insufficiency among nondiabetic patients increased by only about 10%

(from 1860 to 2100 per 100 000 persons) (Table 1). Diabetic patients with chronic renal insufficiency were also about 3-fold more likely to progress to ESRD than nondiabetic patients with chronic renal insufficiency. For each 1000 cases of chronic renal insufficiency in 1991, 38 cases of ESRD developed among diabetic patients in 1996 compared with 11 cases among nondiabetic patients. The only other subgroup with a higher relative risk was black race, which was associated with a 5-fold risk compared with the subgroup of white race (18).

We noted an interesting finding about age, chronic renal insufficiency, and ESRD risk. The prevalence of chronic renal insufficiency among older adults was 10-fold that of younger individuals (10 100 vs. 990 per 100 000 persons) (Table 1). However, younger individuals with chronic renal insufficiency were about 3-fold more likely to progress to ESRD, presumably because of a decreased risk for competing mortality (Table 2). During the study period, it is among the elderly that the growth in ESRD incidence has in particular outpaced growth in chronic renal insufficiency prevalence, reflected by the fact that the highest risk ratio is observed among this subgroup (relative risk, 2.1 [CI, 1.3 to 3.5]) (Table 2).

### Results from a Modeling Approach

We plotted the number of new cases of ESRD among black and white patients, 25 to 79 years of age, in the United States from 1985 to 1996 and found a total projected increase from 25 757 persons to 60 301 persons. When we modeled the slope of the increased ESRD growth, we found an annual unadjusted increase of 8.0% (Figure, model A). Adjustment for population growth and changes in demographic characteristics caused the slope to decrease to 6.9% (Figure, model B). Adjusting for growth in chronic renal insufficiency prevalence during this period

only attenuated the slope further to 6.1% (Figure, model C). Thus, growth in chronic renal insufficiency prevalence seemed to be responsible for only about one tenth of the increase in new ESRD cases.

## DISCUSSION

Our results clearly show that the epidemic of ESRD cannot be explained by the increased prevalence of kidney disease in the United States. We found that increases in ESRD incidence outpaced the increase in chronic renal insufficiency prevalence by 70% during the past 2 decades. By using a Poisson multivariate regression analysis, we found that only about 10% of the growth in ESRD cases could be attributed to increased chronic renal insufficiency in the adult population, an effect smaller in magnitude than that attributed to simple population growth. We conclude that Port's other 2 considerations—more liberal entry into dialysis (and transplant) programs and improved survival from competing causes among persons with chronic renal insufficiency, resulting in greater longevity and eventual need for ESRD (3)—are the dominant contributors to the increasing number of newly treated ESRD cases.

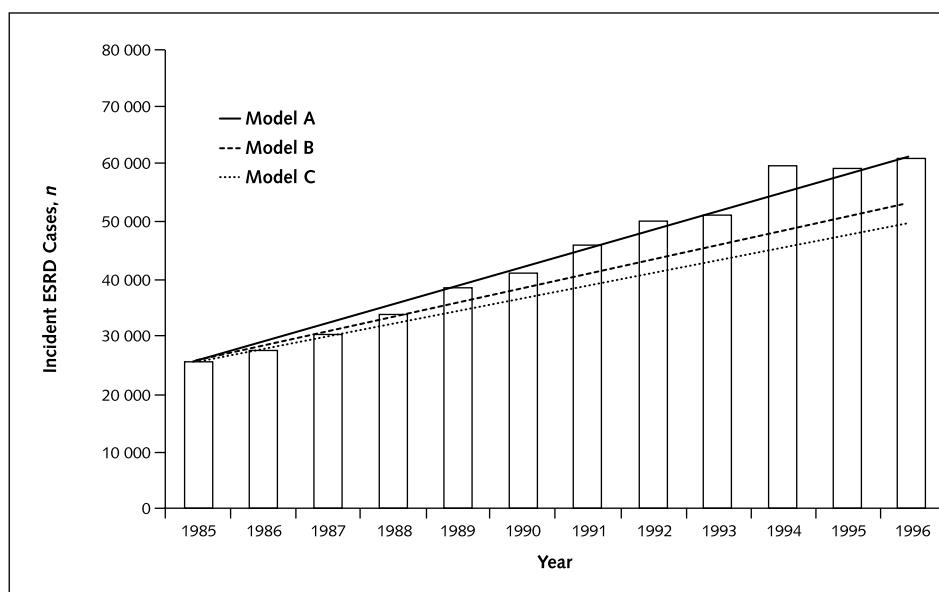
The fact that the increase in ESRD incidence among elderly patients has, in particular, outpaced growth in chronic renal insufficiency prevalence supports the contention that expanded acceptance into treatment programs and improved survival from competing risks are important, since these factors are most relevant among elderly patients. The recent study by Muntner and colleagues (4) found

that improved survival after myocardial infarction and stroke contributed only modestly to the ESRD epidemic. However, these authors did not examine the potential effect of the primary prevention of these conditions and reduced or delayed mortality from cancer and other competing morbid conditions.

In addition to the expansion of dialysis to individuals of older age and more serious comorbid conditions, treatment programs have also liberated the initiation of dialysis to higher GFR levels. In both 1997 and 2001, the influential National Kidney Foundation guidelines recommended that dialysis be initiated at a GFR of 10.5 mL/min per 1.73 m<sup>2</sup> (19, 20). In fact, the mean GRF, estimated by using the MDRD equation, at start of renal replacement therapy in the United States has increased from 7.5 mL/min per 1.73 m<sup>2</sup> in 1995 to 9.3 mL/min per 1.73 m<sup>2</sup> in 2001 (2). As the belief in the beneficial effect of “healthy initiation” of dialysis at a higher GFR before overt uremic symptoms develop (21) is translated into practice, the number of patients with newly treated ESRD will probably increase, since many of these patients might otherwise die of competing causes before dialysis initiation.

An alternative hypothesis to explain the observations in this study is that patients with chronic renal insufficiency in NHANES III sustained more rapid GFR loss than those in NHANES II. This explanation is also compatible with the increase in new ESRD cases outpacing that of chronic renal insufficiency prevalence. We think that this is unlikely, since better control of blood pressure and increased use of angiotensin-converting enzyme inhibitors

**Figure.** Numbers of cases of newly treated end-stage renal disease (ESRD) among black and white patients, 25 to 79 years of age, in the United States from 1985 to 1996.



*Model A.* Observed (unadjusted) rate of increase in incidence (estimated rate, 8.0% per year). *Model B.* Adjusted rate for population growth and demographic characteristics (estimated rate, 6.9% per year). *Model C.* Adjusted rate for population growth, demographic characteristics, and chronic renal insufficiency prevalence (estimated rate, 6.1% per year).

(or angiotensin-receptor blockers) are interventions proven in clinical trials to reduce the rate of GFR loss in patients with chronic renal insufficiency (7). Adults with chronic renal insufficiency in 1991, in contrast to their counterparts in 1978, had better blood pressure control and access to angiotensin-converting enzyme inhibitors. Although more patients with chronic renal insufficiency in 1991 had diabetes mellitus, and diabetic nephropathy may be a more rapidly progressive disease, ESRD outpaced chronic renal insufficiency in both the diabetic and nondiabetic strata. We do not know of any studies from representative, community-based chronic renal insufficiency cohorts that directly compared the rate of loss of GFR in the 1970s versus the 1990s.

To the best of our knowledge, ours is the first study to compare systematically temporal trends in the incidence of treated ESRD relative to the prevalence of chronic renal insufficiency in the United States. Although NHANES II and III and the USRDS registry are the best (in fact, the only) data sources to answer these important public health questions, our methods have several limitations. Serum creatinine level values were missing from approximately one quarter of the NHANES II examinees. However, the 2 leading causes for their absence—loss of specimen in shipping and running out of serum sample—should lead to missing data that either are random (which is addressed by the reweighing procedure) or will probably underestimate the burden of chronic renal insufficiency among NHANES II examinees (because sicker enrollees would presumably have subsatisfactory phlebotomy and smaller volumes of blood specimen). Hence, this should actually bias us against finding that growth in ESRD substantially outpaced growth in chronic renal insufficiency. We could only estimate GFR among NHANES enrollees; however, measuring GFR is impractical in large-scale epidemiologic studies, and important public health and policy decisions are now being based on equation-estimated GFR values (7). The chronic renal insufficiency and ESRD populations could only be linked and broadly described by using the limited data elements common to both NHANES III and USRDS (for example, age, sex, and race), and individual-level data were not available. The number of patients with chronic renal insufficiency sampled in NHANES II in each demographic subgroup limited our ability to perform more extensive modeling. We could not assess secular trends in proteinuria because only dipstick urinalysis was performed in NHANES II, whereas NHANES III quantified proteinuria by using the urine albumin–creatinine ratio (22).

In conclusion, our study provides fresh insights into the epidemiology of kidney disease in the United States. Most patients with chronic renal insufficiency never progress to ESRD. Growth in incident ESRD treatment cases has far outpaced growth in chronic renal insufficiency prevalence, and the increase in chronic renal insufficiency prevalence is, in fact, a minor contribution to the ESRD epidemic. Instead, the ESRD epidemic may reflect larger

social forces, such as patient and physician choices about aggressiveness of providing dialysis. Increased ESRD incidence may also ironically be due to improvements in care—such as initiation of dialysis at higher GFR levels and overall success in reducing or postponing the competing risks for cardiovascular or cancer deaths. The goals of Healthy People 2010 for reducing cases of ESRD will probably not be accomplished simply by interventions aimed at the primary and secondary prevention of kidney disease. We need to broaden our view beyond nephrology and to account for developments in other areas of medicine and larger socioeconomic considerations.

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