Exploring Secular Trends in the Likelihood of Receiving Treatment for End-Stage Renal Disease

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There is a limited understanding of the forces that drive the steady rise in the number of patients who receive treatment for ESRD. It was hypothesized that this is not simply due to increasing prevalence of chronic kidney disease (CKD) or changes in renal failure risk factors in the population from which ESRD cases develop. A noncurrent cohort study was conducted to quantify the change over time (per year) in the likelihood of receiving ESRD therapy in a cohort of 320,252 individuals who volunteered for health check-ups between 1964 and 1985. Initiation of ESRD treatment was ascertained using the US Renal Data System registry through 2000. A total of 1471 cases of ESRD were observed during 8,347,955 person-years of observation, with ESRD cases developing between 1973 and 2000. In unadjusted Cox proportional hazards analysis, individuals who were examined later in time had an 8% per year higher risk for progressing to receive treatment for ESRD (relative risk 1.08; 95% confidence interval 1.05 to 1.11). This temporal trend in risk for future ESRD associated with year of cohort entry (baseline examination) was not explained by increases over time in the prevalence of CKD or risk factors for renal failure. After adjustment for age, gender, race, diabetes, BP, body mass index, education level, smoking status, history of myocardial infarction, serum cholesterol, proteinuria, hematuria, and serum creatinine level, there remained an 8% per year increase in risk (relative risk 1.08; 95% confidence interval 1.06 to 1.11). Among individuals who were examined from the 1960s through the 1980s, those who were examined later were more likely to receive treatment for ESRD. This trend was not accounted for by increasing prevalence of baseline CKD or risk factors for renal failure. These findings should spur further research into other forces that drive the rise in treated ESRD.

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The steady rise in the number of patients who receive treatment for ESRD is a worldwide public health problem (1–4). *Healthy People 2010* lists reducing ESRD incidence as a national health priority. However, our understanding of the relative importance of contributors to the ESRD epidemic remains limited.

We recently noted that through the 1980s, increase in incidence of treated patients with ESRD in the United States greatly outpaced the increase in prevalence of stage 3 or higher chronic kidney disease (CKD; GFR <60 ml/min per 1.73 m^2) (5). A subsequent report showed continued stability in prevalence of individuals with reduced GFR or proteinuria through the 1990s (6).

These observations suggest that in addition to increasing prevalences of known risk factors for ESRD such as decreased GFR, there may be other important factors that contribute to the increasing number of individuals who receive treatment for ESRD. The studies cited in the previous paragraph (5,6), although provocative, are limited by their cross-sectional and ecological nature.

The number of individuals who receive ESRD therapy is a function of temporal trends in the baseline characteristics of the source population, in the relative hazard of developing ESRD independent of baseline characteristics, and in the threshold to initiate therapy for ESRD. We explore here in a large screened cohort with longitudinal follow-up whether there are important secular trends in the likelihood of progressing to receive treatment for ESRD independent of baseline characteristics. The ability to analyze detailed clinical information regarding the source population from which individual patients with ESRD arise represents an advancement over previous ecological studies.

Materials and Methods

Study Population

Details of the study population were described previously (7). This study is based on a large, well-characterized cohort of Kaiser Permanente of Northern California members who participated in the Multiphasic Health Testing Service Program in the Oakland and San Francisco medical centers between 1964 and 1985 (n = 320,252) (8). Kaiser Permanente of Northern California is a large, integrated health care delivery system that currently cares for more than one third of the insured adult population in the greater San Francisco Bay Area (9). The Multiphasic Health Checkup was a voluntary health assessment offered at initial and yearly open enrollment periods (8). Data were

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available for three Multiphasic Health Checkup periods: June 1964 to August 1973 (first period), September 1973 to December 1977 (second period), and January 1978 to March 1985 (third period). The exact components of the screening examinations varied by period depending on administrative considerations as well as what was deemed appropriate screening tests during that time period, but core data elements for this analysis are available for all three periods as described below.

Institutional Review Boards at the collaborating institutions approved the study. As a secondary analysis of existing data, the need for obtaining informed consent was waived.

Assessment of Covariates

Detailed demographic and clinical parameters on the study patients were defined as described previously (7). Medical history data were not available in an electronic format for participants from the second period (September 1973 to December 1977).

Information that was available for defining presence or absence of diabetes varied across the three Multiphasic Checkup periods. Self-report of diagnosis or treatment of diabetes was available in the first and third periods. Blood glucose measurements were available for all periods but were done in the context of oral glucose challenge tests during the first period. In our primary analysis, individuals who had their Multiphasic Checkup examination during the first period (1964 to 1973) were defined as having diabetes using self-report of diabetes. Individuals who had their Multiphasic Checkup examination during the second period (1973 to 1977) were defined as having diabetes when their blood glucose measurements were ≥200 mg/dl because we considered these to be random (nonfasting) measurements; medical history information regarding diabetes status is not available electronically in this period. Individuals who had their Multiphasic Checkup examination during the third period (1978 to 1985) were defined as having diabetes either by self-report or when their blood glucose measurements were ≥200 mg/dl. In sensitivity analyses, we considered a number of alternative definitions of diabetes, including using blood glucose measurement ≥200 mg/dl in addition to self-report in the first period and changing the blood glucose measurement threshold in the second and third periods to 126 mg/dl.

Identification of Outcomes of Treated ESRD and Death

We identified cases of ESRD by matching our cohort (blinded to exposure status) against the nationally comprehensive US Renal Data System (USRDS) ESRD treatment registry data (10). Deaths were ascertained using the California Automated Mortality Linkage System (11). Both ESRD and death were assessed through December 31, 2000.

Statistical Analyses

We first tabulated the crude number of new ESRD cases that arose from this cohort by calendar year of development of ESRD. This univariate analysis is limited because those who started ESRD therapy in any single calendar year are made up of individuals who entered the cohort in different calendar years. For example, of the 26 patients who initiated ESRD therapy in 1985, one was from those who had their baseline Multiphasic Checkup in 1983 (and in their second year of follow-up) and two from those who had their baseline Multiphasic Checkup in 1965 (and in their 20th year of follow-up).

To understand further the underlying temporal trends, we next calculated crude incidence of ESRD by calendar year of cohort entry. Person-time was calculated as years elapsed from baseline date of Multiphasic Checkup until death, development of ESRD, or the end of follow-up on December 31, 2000, whichever occurred first.

The temporal trend that we primarily are interested in is the association between calendar year of cohort entry and risk for eventual ESRD, and this is isolated better by using a Cox model that allows the hazard of development of ESRD to vary by year of follow-up after cohort entry. In univariate Cox proportional hazards analysis, it is not possible to determine whether any increase in ESRD risk among those who were examined later is because those who entered the cohort in later years were more likely to have risk factors for ESRD (*e.g.*, higher baseline prevalence of proteinuria, increased body mass index [BMI]). Our final results therefore are based on multivariable Cox proportional hazards analyses. We determined the independent association between calendar year of cohort entry and risk for ESRD that is not confounded by baseline prevalence of kidney disease and risk factors for kidney failure by adjusting for age, gender, race, diabetes, BP, BMI, education level, smoking status, history of myocardial infarction, serum cholesterol, proteinuria, hematuria, and serum creatinine. All analyses were conducted using SAS (SAS Institute, Cary, NC), and hazard ratios are reported as relative risks.

Data that were available to define diabetes and the degree of missing data varied by period, so our primary analysis consisted of three stratified multivariate analyses—one for each period of Multiphasic Checkup. For multivariable analyses in the second period (1973 to 1977), we did not adjust for education, smoking, and history of myocardial infarction because these data elements were missing for essentially all individuals (Table 1). To obtain an overall estimate of the "year of cohort entry" parameter, we used a fixed-effects meta-analysis approach (Stata Version 9.1; Stata Corp., College Station, TX; command "meta") because individuals who had baseline examinations in the three different time periods can be considered independent samples from three studies of similar design. The Q-statistic was used to test for equality of effects across the three periods.

Because it is possible that the national registry's completeness in capturing ESRD cases nationwide improved through the 1970s, observations might be subject to left truncation. Several left truncation dates were used in sensitivity analyses along with dropping of observed ESRD events before those times (12). We chose the three truncation dates of December 31, 1973; December 31, 1977; and December 31, 1987 to reflect three important milestones, including when the US Congress initially gave patients with ESRD Medicare entitlement, when what is now the Center for Medicare and Medicaid Services began to administer the registry, and when the registry became a core component of the then new USRDS, respectively.

To explore the possibility that risk for acquisition of diabetes after cohort entry was a confounding factor (because this may differ among those who were examined in the 1960s *versus* the 1980s as a result of secular changes in prevalence of obesity), we repeated our analysis and limited it to the subset of individuals who were already known to have diabetes at cohort entry. We also repeated our analysis and limited it to those who were obese at entry (BMI ≥30 kg/m^2). Furthermore, we repeated our analysis among the whole cohort but using as outcome only ESRD cases that were not ascribed to diabetes according to USRDS data.

Secondary Analysis

To explore the impact of any potential improvement in survival from competing causes, we examined the association between calendar year of cohort entry and risk for all-cause mortality by repeating our analysis but using death before ESRD as the outcome (and censoring for ESRD events).

Results

Among 320,252 individuals, the mean age and BP were lower and the proportion of nonsmokers and nonwhite individuals

Table 1. Characteristics of study population (n = 320,252) at baseline examination, stratified by year of examination (year of cohort entry)[a]

Characteristic (Mean ± SD or n [%])	Calendar Year of Multiphasic Health Checkup Examination (Cohort Entry)		
	First Period, 1964 to 1973 (n = 177,570)	Second Period, 1973 to 1977 (n = 66,603)	Third Period, 1978 to 1985 (n = 76,079)
Age (yr)	41 ± 14	35 ± 13	35 ± 13
Women	96,309 (54)	35,061 (53)	41,769 (55)
Race			
white	136,163 (77)	43,274 (65)	42,249 (56)
black	26,505 (15)	14,082 (21)	19,102 (25)
Asian	7,465 (4)	4,418 (6)	6,180 (8)
other	7,409 (4)	5,065 (8)	8,502 (11)
unknown	28 (0.02)	34 (0.05)	46 (0.06)
BMI (kg/m^2)	24.7 ± 4.1	24.3 ± 4.4	24.2 ± 4.6
Height (cm)	167.7 ± 9.6	168.5 ± 9.8	168.2 ± 9.9
Weight (kg)	69.6 ± 14.3	69.4 ± 15.2	68.9 ± 15.6
BMI categories			
underweight	4,401 (2)	2,543 (4)	3,408 (4)
normal weight	100,337 (56)	40,000 (60)	46,393 (61)
overweight	56,861 (32)	17,721 (26)	18,775 (25)
obese class I	12,117 (7)	4,534 (7)	5,205 (7)
obese class II	2,757 (2)	1,261 (2)	1,522 (2)
obese class III	1,097 (1)	544 (1)	776 (1)
Education			
high school or less	87,228 (49)	863 (1)	23,414 (31)
some college	50,397 (29)	744 (1)	22,024 (29)
college grad plus	30,578 (17)	876 (2)	27,184 (36)
unknown	9,367 (5)	64,120 (96)	3,457 (4)
Cigarette smoking history			
never	66,281 (38)	1,109 (2)	36,156 (47)
former	28,901 (16)	480 (0.7)	13,708 (18)
current	67,767 (38)	837 (1.3)	22,542 (30)
unknown	14,621 (8)	64,177 (96)	3,673 (5)
History of myocardial infarction			
no	173,191 (98)	2,412 (4)	70,997 (93)
yes	4,343 (3)	86 (0.1)	2,337 (3)
unknown	36 (0.02)	64,105 (96)	2,745 (4)
Systolic BP (mmHg)	131 ± 21	129 ± 20	124 ± 17
Diastolic BP (mmHg)	77 ± 14	76 ± 12	74 ± 11
Serum cholesterol (mg/dl)	221 ± 45 (missing 6.6%)	202 ± 40 (missing 0.3%)	204 ± 45 (missing 0.05%)
Urine protein			
negative	168,226 (94)	65,507 (98)	73,635 (97)
trace	4,623 (3)	954 (1)	1,430 (2)
1 to 2+	4,210 (2)	100 (0.2)	883 (1)
1 to 3+	511 (0.3)	42 (0.1)	131 (0.2)
Urine hemoglobin			
negative	169,994 (96)	64,470 (97)	70,161 (92)
small	5,521 (3)	1,603 (2)	3,454 (4)
moderate	1,436 (1)	414 (0.6)	1,243 (2)
large	619 (0.4)	116 (0.2)	1,221 (2)
Serum creatinine (mg/dl)	0.98 ± 0.27	0.92 ± 0.18	0.91 ± 0.21
Self-report of diabetes			
no	173,462 (98)	2,443 (4)	71,771 (94)
yes	4,072 (2)	55 (0.1)	1,563 (2)
unknown	36 (0.02)	64,105 (96)	2,745 (4)
Blood glucose level	168 ± 52 (missing 0.07%)	111 ± 28 (missing 0.003%)	94 ± 24 (missing 0.05%)
Blood glucose measured in the context of oral glucose challenge test	Y	N	N

[a]BMI, body mass index.

was higher in the later Multiphasic periods (Table 1). After 8,347,955 person-years of observation, there were 1471 cases of ESRD and 56,336 deaths (55,425 of which were before onset of ESRD). Individuals who were examined in the first period (1964 to 1973) contributed 842 cases of ESRD and 5,275,957 person-years of follow-up. Those who were examined in the second period (1973 to 1977) contributed 322 cases and 1,606,809 person-years of follow-up. Those who were examined in the third period (1978 to 1985) contributed 307 cases of ESRD and 1,465,189 person-years of follow-up. In the individuals who received ESRD therapy, the mean duration between cohort entry and ESRD was 21 ± 8 (SD) years (median 21 yr; interquartile range 16 to 27 yr).

Temporal Trend in Risk for Receiving ESRD Treatment

Ninety percent of the documented cases of treated ESRD occurred after 1983, and 80% of the cases occurred after 1987 (Table 2). The crude incidence of ESRD increased from 14 per 100,000 person-years among individuals who were examined in 1964 to 34 per 100,000 person-years for those who were examined in 1985 (Figure 1).

In univariate Cox proportional hazards analysis, individuals who were examined in later years had on average a higher risk for progression to receive treatment for ESRD (Table 3). When we examined clinical covariates that may be confounders, as expected and as previously reported (7,13–20), advanced age, black and Asian races, diabetes, proteinuria, higher serum creatinine, elevated BP, and elevated BMI all were significant independent predictors of ESRD. However, even after adjustment for these baseline predictors of ESRD, within each Multiphasic period, individuals who were examined in later calendar years had a higher likelihood of eventually receiving ESRD treatment compared with individuals who were examined earlier. The relative risks (RR) were 1.08 (95% confidence interval [CI] 1.05 to 1.11), 1.09 (95% CI 0.99 to 1.20), and 1.11 (95% CI 1.04 to 1.18) per year within the first, second, and third periods, respectively (Table 3). The summary estimate from the meta-analysis indicated that, independent of baseline characteristics, individuals who were examined in later calendar years were on average 8% more likely per cohort entry year to receive treatment for ESRD eventually (RR 1.08; 95% CI 1.06 to 1.11; Q statistic = 0.69; $P = 0.71$).

Table 2. Distribution of year of incident ESRD case originating from cohort

Year of ESRD Development	*n*	Cumulative *n*	Cumulative %
1973	1	1	0.07
1974	2	3	0.20
1975	5	8	0.54
1976	5	13	0.88
1977	16	29	1.97
1978	6	35	2.38
1979	16	51	3.47
1980	13	64	4.35
1981	20	84	5.71
1982	21	105	7.14
1983	22	127	8.63
1984	24	151	10.27
1985	26	177	12.03
1986	34	211	14.34
1987	48	259	17.61
1988	38	297	20.19
1989	58	355	24.13
1990	63	418	28.42
1991	86	504	34.26
1992	81	585	39.77
1993	79	664	45.14
1994	115	779	52.96
1995	102	881	59.89
1996	96	977	66.42
1997	113	1090	74.10
1998	141	1231	83.68
1999	105	1336	90.82
2000	135	1471	100.00

Sensitivity analyses using alternative definitions of diabetes yielded a very similar estimate of 9% increase in risk for ESRD per calendar year (RR 1.09; 95% CI 1.06 to 1.12). Similar results were observed after taking into account possible bias as a result of left truncation by analyzing only cases of ESRD that occurred after three separate dates—an 8% increase per cohort entry year in risk for ESRD was observed using December 31, 1973, as the truncation date (RR 1.08; 95% CI 1.05 to 1.11); 7% increase in risk per year using December 31, 1977 (RR 1.07; 95% CI 1.05 to 1.10); and 6% increase in risk per year using December 31, 1987 (RR 1.06; 95% CI 1.03 to 1.10).

When we limited our analysis only to individuals who had known diabetes or obesity at cohort entry, a similar magnitude of increase in risk for treated ESRD over time was observed (RR 1.08 [95% CI 1.01 to 1.16] and RR 1.12 [95% CI 1.07 to 1.17], respectively; Table 4). In addition, the same magnitude of increase in risk for treated ESRD over time was observed when only cases of ESRD that were not ascribed to diabetes were examined (RR 1.09; 95% CI 1.05 to 1.12; Table 4).

Secondary Analysis of Temporal Trend in Risk for Mortality

We did not detect any consistent temporal trend toward lower overall mortality among those who had their Multiphasic Checkup examinations in later calendar years. In the first period, individuals who entered the cohort in later years seemed to have a slightly higher adjusted risk for death (RR 1.02; 95% CI 1.02 to 1.03). This trend was weaker and was not statistically significant in the second (RR 1.01; 95% CI 0.995 to 1.03) or third (RR 0.99; 95% CI 0.98 to 1.004) period. There also was no temporal trend toward lower mortality among the subset of individuals with known diabetes at cohort entry (data not shown).

Discussion

Our results show that a 50-yr-old white woman who had diabetes and certain levels of BP, serum creatinine concentration, and proteinuria and presented in the 1980s would be

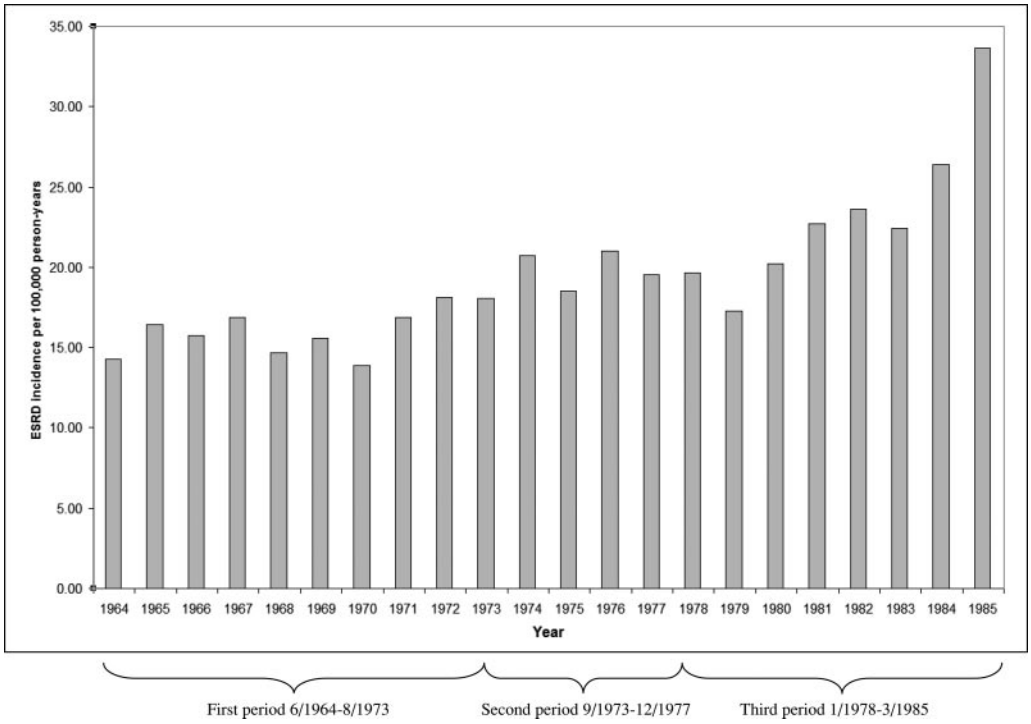

Figure 1. Crude incidence (per 100,000 person-years) of new cases of treated ESRD through 2000 by year of cohort entry (year of baseline Multiphasic Checkup Examination).

Table 3. Risk for progression to receive treatment for ESRD among individuals who were examined in later years compared with those who were examined in earlier years before and after adjustment for baseline risk factors[a]

Time Period	Unadjusted (Crude Observed) RR (95% CI) per Year of Cohort Entry	Adjusted RR[b] (95% CI) per Year of Cohort Entry
First period (1964 to 1973)	1.07 (1.04 to 1.10)	1.08 (1.05 to 1.11)
Second period (1973 to 1977)[c]	1.04 (0.95 to 1.14)	1.09 (0.99 to 1.20)
Third period (1978 to 1985)	1.12 (1.06 to 1.19)	1.11 (1.04 to 1.18)
Summary	**1.08 (1.05 to 1.11)**	**1.08 (1.06 to 1.11)**

[a]CI, confidence interval; RR, relative risk.
[b]Adjusted for age, gender, race, diabetes, BP, BMI, education level, smoking status, history of myocardial infarction, serum cholesterol, proteinuria, hematuria, and serum creatinine level.
[c]Not adjusted for education level, smoking, and history of myocardial infraction in the second period.

much more likely to go on to receive treatment for ESRD compared with another 50-yr-old white woman who had all of the same clinical characteristics and presented in the 1960s. These individual-level prospective data are consistent with previous cross-sectional and ecological studies showing an apparent dissociation between increase in incidence of treated ESRD and prevalence of CKD (5,6).

Potential Explanations

One potential explanation for these observations is that improved survival from competing causes resulted in greater longevity and survival to reach ESRD (21). Although this is not supported by our analysis of temporal trend in mortality within our cohort, we do not believe that our data provide definitive evidence against this hypothesis, because only deaths that occurred within California were counted and this may have introduced some ascertainment bias. Also, we did not capture potentially important baseline predictors of mortality (*e.g.*, cancer, severe pulmonary disease). A second possibility is that individuals who were examined in the 1980s experienced more rapid loss of GFR than individuals who were examined in the 1960s. However, one would expect that individuals who were examined later in time would have had greater access to angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and would have had their hypertension treated more aggressively—interventions that have been proven to reduce the rate of GFR loss in large, randomized, controlled trials (22–24). There is, in fact, evidence that improvements in med-

Table 4. Risk for progression to receive treatment for ESRD among individuals who were examined in later years compared with those who were examined in earlier years independent of baseline risk factors among individuals with known diabetes at baseline, among individuals with established obesity at baseline, and among all individuals but using as outcome cases of ESRD that were not ascribed to diabetes

Time Period	Adjusted RR[a] (95% CI) per Year of Cohort Entry		
	Among Individuals Who Were Known to Have Diabetes at Time of Baseline Multiphasic Checkup[b]	Among Individuals with Established Obesity (BMI ≥30 kg/m^2) at Time of Baseline Multiphasic Checkup	Among Entire Cohort with Outcome of ESRD not Ascribed to Diabetes
First period (1964 to 1973)	1.10 (1.00 to 1.21)	1.12 (1.06 to 1.18)	1.07 (1.03 to 1.11)
Second period (1973 to 1977)[c]	1.11 (0.89 to 1.38)	1.09 (0.92 to 1.29)	1.02 (0.90 to 1.16)
Third period (1978 to 1985)	1.04 (0.93 to 1.17)	1.11 (0.99 to 1.25)	1.19 (1.10 to 1.29)
Summary	**1.08 (1.01 to 1.16)**	**1.12 (1.07 to 1.17)**	**1.09 (1.05 to 1.12)**

[a]Adjusted for age, gender, race, diabetes, BP, BMI, education level, smoking status, history of myocardial infarction, serum cholesterol, proteinuria, hematuria, and serum creatinine level.
[b]Not adjusted for diabetes in model stratified by diabetes status.
[c]Not adjusted for education level, smoking, and history of myocardial infraction in second period.

ical care, such as better glycemic control among patients with diabetes, indeed has reduced the likelihood of renal failure in that subset of patients (25,26). However, definitive evidence for or against this hypothesis is not available, because no studies from representative, community-based CKD cohorts have compares directly the rate of loss of GFR in the 1960s and 1970s *versus* the 1980s and 1990s. A third possibility is that individuals who were examined later in time were more likely to develop obesity and diabetes between cohort entry and the development of ESRD, which would confound the observed association. However, we detected the same temporal trend in individuals who had known diabetes or obesity at cohort entry. Furthermore, the same temporal trend was observed when we limited our outcome to only cases of ESRD that were not ascribed to diabetes.

Our data are consistent with the hypothesis that an important but underappreciated contributor to the increase in number of observed cases of treated ESRD is more liberal entry into dialysis (and transplant) programs. This is congruent with data from other sources. For example, from 1995 to 2004, the mean estimated GFR at the start of renal replacement therapy in the Unite States increased from 7.5 to 10.0 ml/min per 1.73 m^2 (27). Similarly, from 1992 to 2001, serum creatinine concentration at the start of ESRD treatment decreased in the Australia and New Zealand Dialysis and Transplant registry from 1000 μmol/L (11.3 mg/dl) to 750 μmol/L (8.5 mg/dl) (28). If this explanation is correct, then there obviously are important implications. The "epidemic" of treated ESRD ironically may be, in part, a result of attempts to broaden access to care (*e.g.*, to frail patients with more comorbid conditions [29]) and to improve care (*e.g.*, *via* more "timely" initiation of dialysis at higher GFR levels [30]).

Implications

The increasing number of patients who are being treated for ESRD is one of the biggest public health challenges in nephrology. To our knowledge, this study is the first large-scale investigation with individual-level data spanning several decades to explore the relationship between temporal trends in baseline renal function and risk factors for renal failure in a known source population and subsequent risk for ESRD. The new insight from this study is that even after taking into account temporal changes in the source population baseline risk profile, there still are important secular trends in the likelihood of progressing to receive treatment for ESRD.

What are the implications of our finding? From a public health and clinical perspective, we believe that these data underscore the need to evaluate how much of the "ESRD epidemic" is actually driven by practice pattern changes in initiating renal replacement therapy at higher levels of GFR. As discussed, the proponents of "timely" initiation of dialysis have influenced clinical practice, although there is limited evidence to support the benefits of this approach (31,32). The potential downsides of systematically starting ESRD therapy at higher levels of GFR in terms of increasing individual burden and societal costs deserves further scrutiny.

For policy makers, if initiating patients on dialysis therapy at an earlier stage of disease indeed is clinically beneficial, then this must be taken into account when evaluating the appropriateness of and the likelihood of reaching public health goals such as that set forth in *Health People 2010* to reduce the number of new ESRD patients to 21.7 cases per 100,000 population (from 28.9 per 100,000 reported in 1997) (33). Similarly, health care planners would need to realize that even full implementation of renoprotective therapies such as angiotensin blockade may not translate into as great a benefit as projected in terms of reducing number of individuals who ultimately need ESRD therapy (34).

For researchers, we hope that our results will stimulate research into other potential factors that link CKD to ESRD. For example, recent studies show that the incidence of dialysis-requiring acute renal failure has increased dramatically in the past two decades (35,36). It is known that some patients who have acute renal failure do not recover renal function (37). Few studies have investigated the connections among CKD, acute

renal failure, and ESRD, and acute renal failure may be an underrecognized contributor to ESRD.

Strengths and Limitations

An important strength of this study compared with previous reports (5,6,26,38–40) is that we analyzed individual-level data spanning several decades among a well-characterized source population from which ESRD cases were drawn. A limitation was the inclusion of only individuals who volunteered for screening examination in a single health care system in California, so our results may not be completely generalizable to other geographic areas or health systems. Bias from selection into the cohort over time of individuals who were more likely to develop ESRD because of some unmeasured baseline characteristic is possible but unlikely because we adjusted for all of the major known risk factors for ESRD. As mentioned, deaths from any cause were ascertained using state death certificate files, which may not capture individuals who migrated outside California, but this was not the main outcome of our study. ESRD capture, however, was comprehensive using a national registry. We did not have information regarding use and type of antihypertensive and hypoglycemic medications. We also did not have longitudinal data describing the period between initial examination and development of ESRD, so we are unable to evaluate the role of any subsequent nephrotoxic insults or treatments that aimed to retard renal disease progression.

Conclusion

An individual with a certain set of clinical characteristics from the 1980s was more likely to go on to receive treatment for ESRD compared with an individual with identical risk factors from the 1960s. These and other results (5,6) strongly suggest that increasing incidence of treated ESRD cannot be accounted for entirely by there simply being more patients with low GFR or the increasing prevalence of risk factors for kidney failure in the source population. Our study highlights that factors other than known predictors of ESRD are contributing to the increasing number of patients who initiate ESRD therapy, which has clinical, public health, policy, and research implications. In particular, research is needed to quantify the contribution of earlier initiation of dialysis and other possible factors such as acute renal failure to the ESRD epidemic. The importance of these questions on an international level is underscored by recent data showing that ratio of ESRD incidence to CKD prevalence is much higher in the United States than in Europe (41–43).

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Disclosures

None.

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