Trends in Incidence of Kidney Failure and Survival on Dialysis

by

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Abstract

Background and Rationale

End-stage kidney disease (ESKD) patients are typically treated through either maintenance dialysis or transplantation. Age-adjusted mortality rates of these patients have fallen over the past twenty years, but the rates remain much higher than in the general population. The incidence of patients starting ESKD treatment has risen over the same period, and both trends will significantly impact future ESKD prevalence. Understanding these trends is important because of the impact of ESKD on morbidity, mortality, quality of life, healthcare utilization, policy, and costs, especially the cost to Medicare.

Aims

The aims of this dissertation were to:

1) Gain an understanding of the impact of past changes in measures of adherence to current dialysis practice recommendations on patient survival in three geographic regions: the US, Europe, and Japan. We hypothesized that changes in these nephrology practice measures would explain some of the trends towards improved adjusted survival.
2) Simulate the incidence and prevalence of ESKD in the US, based on population factors including race, age, population size, obesity, hypertension, and diabetes, and ESKD factors including death rates among ESKD patients.

3) Project the incidence and point prevalence of ESKD in the US through the year 2030, based on accurately modeled population trends and a broad, yet plausible range of future changes in population obesity and ESKD death rates.

Methods

Aim 1 was addressed using data from the international Dialysis Outcomes and Practice Patterns Study (DOPPS) on adult in-center hemodialysis patients. Mediation analyses were conducted using time (1999 to 2015) as the "exposure," various nephrology practice measures as potential mediators that might explain temporal trends in the outcome, and patient survival as the outcome.

Aim 2 was addressed using a simulation model to simulate transitions between population prevalence of obesity, diabetes, hypertension, and ESKD incidence for age- and race-specific demographic groups, using smoothed estimates of time-varying parameters for incidence of diabetes, death rate among patients with diabetes, ESKD incidence, and hypertension incidence. Inputs included annual data from 1980-2013, from the Centers for Disease Control National Health and Nutrition Examination Survey (CDC NHANES), the Centers for Disease Control and Prevention National Health Interview Survey (CDC NHIS), the United States Renal Data System (USRDS), and the US Census. Estimates were calibrated via Nelder-Mead optimization of the sum-of-squared errors in yearly ESKD and diabetes incidence, as predicted by public population data.

The model built for Aim 2 was used to address Aim 3 by projecting future trajectories of incidence rates and prevalence of ESKD, using different patient populations and smoothing methods to test the sensitivity of the model's predictions to different inputs. The projections were tested based on assumed obesity rates that either continue to rise to nearly half the population by

2030 versus assumed obesity rates that fall below 30% by 2030. The projections were also tested based on assumed death rates among ESKD patients that either remained similar to current rates or continued to fall by approximately 40% by 2030. These ranges were chosen to be wide enough to include all plausible future trajectories of these important contributors to ESKD incidence and prevalence.

Results

Aim 1: Among adult hemodialysis patients during the 1999-2015 period, age adjusted survival has improved by 24% per decade in Europe, 9% in Japan, and 45% in the US. Based on the DOPPS sample, changes in practice measures explain 12%/decade (95% confidence interval +/-8%) longer survival in Europe, primarily through Kt/V and phosphorous control. In other words, if the median European dialysis patient lived 4.4 years in 1999, then the practice changes in Europe would have resulted in a similar patient living 4.4*1.12 = 4.9 years in 2009. Similarly, changes in practice measures explain a 9% (+/-5%) per decade survival improvement in Japan, primarily through the dose of dialysis (Kt/V) and intra-dialytic weight gain (IDWG), and a 26% (+/-9%) per decade survival improvement in the US, primarily through fistula use and phosphorous control. While these inferences are drawn from observational data, limiting our ability to draw conclusions about causal relationships, these factors have clinical justification for their associations with mortality, and these associations have tended to be reasonably consistent in analyses of independent datasets.

Aim 2: Age- and race-specific ESKD incidence rates and prevalence can be modeled for most age/race groups from 1980 through 2013, and the simulated frequencies that result from current population aging and obesity trends follow past age-specific and overall incidence trends.

Aim 3: ESKD incidence and prevalence will continue to rise through 2030 primarily due to demographic trends, such as the aging US population. The projected number of patients diagnosed with incident ESKD in 2030 is 137,000-151,000, a 19-32% increase from 2013, depending on obesity trends. The crude (unadjusted) incidence rate will rise to 381-421 per million/year, a 5-16% increase. The projected number of patients with ESKD in 2030 is 794,000-1,219,000, a 22-88% increase, depending on trends in obesity and ESKD death rates through 2030.

Conclusion

Evidence-based practices appear to explain a substantial proportion of the decline in lower death rates among hemodialysis patients in the US, several European countries, and Japan. Current demographic trends indicate that despite possible decreases in ESKD incidence within age and race groups, possibly due to advances in treatment, we will have an expanding, increasingly older ESKD population in the US. If we expect to continue current trends in improving the experience of these patients, we will need to not only continue to investigate and apply practices that result in improved outcomes, but we should also plan to have sufficient resources in place to care for the consequent increase in the number of patients requiring ESKD care.

Chapter 1 Introduction

There have been sustained international efforts to create evidence-based guidelines for clinical practices used to care for hemodialysis patients. Extensive treatment guidelines have been published by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI), the Kidney Disease: Improving Global Outcomes (KDIGO), the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA), and the Japanese Society for Dialysis Therapy, among other organizations. These organizations have carefully weighed the available evidence from clinical trials, observational studies, and expert opinion when creating their guidelines, and this effort has been an important contribution to clinical practice.

The gap in the literature that the first part of this dissertation addresses is to evaluate past effects of changes in practice measures that reflect adherence to recommendations for the care of hemodialysis patients in the US, several European countries, and Japan. These analyses were conducted using data from the Dialysis Outcomes and Practice Patterns Study (DOPPS). The fact that DOPPS has consistently collected data across these countries over the period studied (1999-2015) makes it uniquely suited to examining long-term trends in practices and patient outcomes. Using the DOPPS data, we can see that there have been measureable improvements in case-mix-adjusted hemodialysis patient survival, and these can be linked to trends in measures of adherence to evidence-based practice recommendations.

The fact that dialysis patient and transplant recipient lifespans have generally been improving is good news for patients treated for end-stage kidney disease (ESKD), but this trend,

along with changes in incidence, possibly reflecting changes in treatment and population demographics, have made it difficult to accurately project future trends in the size of the ESKD population. These predictions for this sizeable, expensive patient population are important for resource allocation and planning. Although ESKD patients represent 1% of the Medicare population, they account for 7% of Medicare's expenditures, and their prevalence has been increasing. In 1980, there were about sixty thousand ESKD patients in the United States; at the end of 2014, there were 661,648, and annual costs exceeded $30 billion.

Increasing patient lifespan is not the only factor making projections complex. Demographic trends in age and race can influence ESKD incidence and prevalence. The obesity epidemic has been especially severe in the United States, and the impact of this epidemic on diabetes and hypertension, two of the primary causes of ESKD, are very likely to impact future ESKD incidence. The second chapter in this dissertation attempts to discover whether population data can adequately model ESKD incidence and prevalence through 2013, and the third chapter attempts to use this model to project future trends in the ESKD population. How large is the ESKD population likely to get in the United States under various projections of population obesity and ESKD mortality?

The aims of this dissertation were thus to:

1) Describe changes in mortality among hemodialysis patients and estimate the impact of changes in adherence to current practice recommendations on patient survival in three regions: the US, Europe, and Japan.
2) Simulate the incidence and prevalence of ESKD in the US, based on population factors including race, age, population size, obesity, hypertension, and diabetes, and ESKD factors including death rates.

3) Project the incidence and point prevalence of ESKD in the US through 2030, based on modeled population trends and a broad, yet plausible range of future changes in population obesity and ESKD death rates.

Chapter 2 Explaining international mortality trends through changes in practices involving hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Abstract

Background

Dialysis Outcomes and Practice Patterns Study (DOPPS) data show that age-adjusted hemodialysis patient survival has improved since 1998 in three geographic regions: US, Japan,

and four European countries (Germany, Italy, Spain, and the UK). During this period, there have been changes in adherence to practice recommendations, which may have influenced these survival trends. This paper uses product-method mediation analyses to quantify the impact of the changes in adherence to current practice recommendations on patient survival in these three geographic regions.

Methods

DOPPS collects international data on in-center hemodialysis patients. These analyses used DOPPS data from five prevalent cross-sections, taken once per study phase or about every three years between 1999 and 2015. Survival was modeled using an accelerated failure time model with adjustments to account for trends in demographic and comorbid factors. Sixteen measures of dialysis practices were examined; eleven of which were excluded due to exhibiting no substantial trend or an inconsistent or weak effect on mortality in these data. Product-method mediation analyses were conducted using DOPPS phase as a measure of calendar time as the exposure, various practice measures as potential mediators, and patient survival as the outcome. Sensitivity analyses with varying patient populations and adjustments were also conducted.

Results

Among adult hemodialysis patients, age-adjusted survival has improved by 24% per decade in Europe, 9% in Japan, and 45% in the US. Improvements in adherence to recommended practices, as reflected by the practice indicators for dialysis dose (Kt/V), fistula use, hemoglobin within target, inter-dialytic weight gain (IDWG), and phosphorous regulation may explain some of the improvement in survival. Using data from the DOPPS sample, these measures explain 12% per decade (95% confidence interval +/-8%) longer survival in Europe primarily through

Kt/V and phosphorous control, 9% per decade (+/-5%) longer survival in Japan primarily through Kt/V and IDWG, and 26% per decade (+/-9%) longer survival in the US primarily through fistula use and phosphorous control (Figure 2.5), with some variation in these estimates by age, sex, and vintage. These numbers indicate that the changes in practice explain substantial improvements in survival. For example, if a median European dialysis patient lived 4.4 years in 1999, then the practice changes in Europe should have resulted in a similar patient living 4.4*1.12 = 4.9 years in 2009. Other factors examined generally made much smaller contributions.

Conclusion

While different regions have had different trends in these performance measures, the changes in Kt/V, fistula use, hemoglobin, inter-dialytic weight gain, and phosphorous can explain a substantial proportion of the survival improvement seen in the US, Japan, and the four European countries studied. These results suggest that future improvements in patient survival will likely result from continued improvement in adherence to evidence-based recommendations.

Background

Patient survival on dialysis is much lower than survival among the general population and among many patient populations with chronic diseases, but the trends among these populations have been generally towards improved survival.[1] In the United States (US), patient survival has been improving among hemodialysis patients. Age, sex, race, ethnicity, primary diagnosis, and patient-vintage-adjusted mortality rates fell 31% between 1999 and 2014 and age-adjusted mortality rates fell 17% in the general population over the same period.[2],[3]

Case-mix-adjusted mortality rate in DOPPS has historically been higher in the US than in Europe or Japan, although in recent phases the US and European rates are much closer. Patient population and clinical practices have changed over time. We have evaluated the effects of case mix and practice patterns on trends in mortality rates across three regions using a prospective cohort study design.

A number of practice goals have been identified by various international organizations. The recommendations published by organizations such as Kidney Disease Improving Global Outcomes (KDIGO), Kidney Disease Outcomes Quality Initiative (KDOQI), the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) and the Japanese Society of Dialysis and Transplantation (JSDT) are reviewed and improved over time.. These organizations have recommended the minimum delivered Kt/V to be 1.2.[4, 5] Fistulas should be used for dialysis access.[6] These organizations have also indicated the dangers of poor fluid volume control, suggesting among other practices that patients limit sodium intake in part to help control intra-dialytic weight gain (IDWG).[7] Prior research has recommended limiting IDWG to 5.7% of the patient's body weight or less.[8] The JSDT recommended in 2006 that serum phosphorous levels should be between 3.5-6 mg/dl,[9] while KDIGO recommended in 2015 that this level be between 3.5-5.5 mg/dl,[10] We have used consistent thresholds in these analyses that reflect the preponderance of these recommendations over this time period and current research.

The goal of this study was to identify the practices that explain as much of the case-mix-adjusted mortality improvement as possible within each global region (the US, Japan, and four

European countries treated as a single region: Germany, Italy, Spain, and the UK) . We hypothesize that changes in measures of adherence to recommended practices could explain much of the decline in case mix-adjusted patient survival.

Methods

Data

DOPPS is a prospective cohort study of adult (≥ 18 years of age) in-center hemodialysis patients from selected facilities in each country.[11,12] We used 1999-2015 DOPPS data from five study phases: phase 1 (1999-2001), phase 2 (2002-04), phase 3 (2005-08), phase 4 (2009-11) and phase 5 (2012-15). We limited analyses to hemodialysis facilities in Germany, Italy, Japan, Spain, the UK, and the US, as these were the countries that consistently participated in all of the first five phases of DOPPS. Many of the 500500 facilities in these countries continued to participate across multiple study phases; however, follow-up for survival analyses within each phase was censored at the end of the phase.

Patients were chosen from prevalent cross-sections taken at the start of each three-year study phase, and baseline characteristics and comorbid data were obtained as of these cross-sections. Time at risk started at the point of baseline data collection within each phase and continued until the earliest of death or up to 7 days after departure from facility for kidney transplantation, change of treatment modality, withdrawal from dialysis, return of renal function, or transfer to another facility. Follow-up time was censored at the end of each study phase for those who did not depart from the facility, with follow-up from phase 5 ending in June of 2015.

Potential facility-level measures of practices considered as mediators included, Kt/V (>1.2, per KDOQI guidelines[13]), fistula v. graft v. catheter use, albumin (g/dl), hemoglobin (10-12 g/dl), average post-dialysis weight (up to one week's worth of measurements), inter-dialytic weight gain (<5.7% of patient weight), serum phosphorous (< 6 mg/dl), ferritin (200-500 ng/ml, per KDOQI recommendations[14]), parathyroid hormone (PTH) level < 600 pg/mL,[15] average pre-dialysis systolic blood pressure (mmHg) during all three sessions in a week, average post-dialysis systolic blood pressure (mmHg) averaged over up to one week (pre- and post-dialysis), dialysis session length (min), prescribed dialysate sodium (mmol/L), prescribed dialysate potassium (mmol/L), serum sodium (mEql), number of patients per nurse, and number of patients per non-nurse staff. These factors were considered as the percentage of sampled patients within range or the facility mean if no range is applicable, which is based on a combination of recommendations and clinical judgement. Associating each patient with the facility-level practice measures derived from the sampled patients helped avoid treatment by indication bias[16], as well as allowing sensitivity analyses using the census of patients (not just the sample) within each facility. Only facilities with at least 10 patients with non-missing data for each potential mediator were included in the analyses.

An indicator variable for US large dialysis organizations was included to adjust for differences resulting from inconsistencies across phases in the sampling and data collection for this subset of the United States sample.

Figure 2.1 lists the inclusion criteria and resulting sample size. Limiting the analyses to facilities within the target countries with sufficient follow-up and patient data collection

eliminated 18% of the sample, primarily due to the requirement for at least 10 patients within each facility having each of the practice measures. Sampled patients have much more data collection, e.g. comorbid conditions, than non-sampled patients. The resulting census of 88,158 patients and DOPPS sample of 31,051 patients were used for the mediation analyses.

Statistical analysis

Calendar time should not be directly causing patient survival to change except through mediators; e.g. changes in the patient population, dialysis practices, or in general patient health. Dialysis practice measures were evaluated as potential mediators using the product method (Figure 2.2) in order to determine how changes in modifiable practices may have affected patient survival trends. We evaluated these potential mediators using the relationship between the DOPPS phase from which each prevalent cross-section was collected versus patient survival. This was performed separately for each region, as different practices may have affected patient survival within each region, and using different patient populations and sets of confounding factors as sensitivity analyses. The primary result of the mediation analysis used in this paper was the estimate of the indirect effect; i.e. the 'effect' of calendar time through the practice measures hypothesized to be mediators. The remaining unexplained direct effect was assumed to reflect unmeasured predictors of survival that might also be changing over time.

Accelerated failure time (AFT) models with a generalized gamma-distributed baseline were used to model patient survival (or relative life expectancy) from the baseline (cross-section) start of each phase.[17] We chose the AFT model due to the fact that mortality is not likely to be rare enough in the dialysis population to produce unbiased estimates of the indirect effect using a

Cox model.[18] A positive coefficient for a predictor indicates longer expected average survival; a negative estimate indicates shorter expected average survival. The coefficient (beta) for a binary factor is the log of the ratio of the expected survival for patients with the factor to the expected survival for patients without that factor, holding all other factors in the model constant. For continuous predictors, the coefficients can be interpreted as the log of the proportionate change in expected lifespan (or life expectancy) associated with a 1-unit change in the predictor.

Linear regressions on each factor with phase as a predictor were used to estimate trends in the case mix and treatment factors (e.g. age, diabetes, fistula use, etc.).

Some of the covariates, such as the comorbid factors, had up to 5% missing data in these analyses. Missing data were imputed using the SAS multiple imputation procedure with the fully conditional specification option, which achieves satisfactory results with fewer iterations than Markov chain Monte Carlo (MCMC) methods.[19],[20] Imputation was carried out within each bootstrapped replicate dataset; this method produces valid estimates of the confidence intervals.[21] Residual urine volume was not imputed, as the distribution of patient vintage among patients with missing residual urine volume data was much more similar (supplemental Figure 2.5) to that of patients without residual urine volume. We believe that this indicated that this variable might have been more likely to be missing when patients had no residual urine volume, which means that we could not assume it was missing at random. Instead, we imputed a residual urine volume of <200 ml/day when this variable was missing and conducted sensitivity analyses with and without residual urine volume as a covariate.

Mediation analyses of each potential mediator were carried out using the product-method mediation approach.[22] The major exposure/predictor variable was the indicator for each DOPPS phase (1-5 for each time interval shown in Table 2.1 between 1999-2015) for describing the temporal trend, and the outcome was all-cause mortality during each phase. Errors in the model parameter and mediation effect estimates were computed using a bootstrap approach (200 iterations/model).[23] The assessment of the collective indirect effects of multiple potential mediators simultaneously was performed using the product method described by Vanderweele (2015)[24], which allows for estimation of the collective indirect effect by adjusting the estimates of each potential mediator's effect for the other potential mediators. [25] The collective effect can thus be expressed as a summation of the product-method estimates on the log scale. Figure 2.2 illustrates the directed acyclic diagram motivating the mediation analysis, as well as providing the survival model equation and the mathematical description of the product method. The product method was chosen in part due to the fact that it requires fewer assumptions for unbiased estimates when performing survival analysis on censored data than other choices, such as the difference method.[26] A weakness of the product method is the fact that descriptions of the mediation effect as a proportion of the overall effect can be unstable, especially when the confidence interval of the overall effect approaches zero.[27] For this reason, we have avoided calculating estimates of the proportion of the overall survival trend explained by practice measures in this manuscript.

Each model was calculated separately based on patients enrolled in the DOPPS and based on each DOPPS facility's census of patients; in both cases, the prevalent cross-section at the beginning of each DOPPS phase was used. Each model on the sample controlled for patient

factors (case-mix) that have been found to be predictive of mortality in prior studies: age, race (black v. other races, except in Japan in which there were too few black patients), sex, 13 comorbid conditions (coronary artery disease, cancer, cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastro-intestinal bleeding, hypertension, lung disease, neurological disorder, psychiatric disorder, peripheral vascular disease, and recurring cellulitis), BMI, years on dialysis as of the time each cross-section was taken, urine volume (<200 v. 200+ mL/day), and an identifier for US facilities where data collection in later phases came from electronic health records. In a few of the Japan-specific models where there were relatively few deaths, variables with unstable estimates in too many of the imputed bootstrapped iterations were left out of the model. Each model involving census data included covariates for age, race, sex, vintage, and data collection protocol. Due to convergence issues arising from a relatively small number of events (94), the Japan model limited to sample patients with less than one year on dialysis at baseline was run with a reduced list of confounding factors; the estimates remained unstable despite this reduced model, and were excluded from the results presented below.

Mediation analyses were conducted using varying lists of potential mediators. Selection of the specific set of mediators for this manuscript were based on the magnitudes of estimated effects of the potential mediators on mortality, the consistency of those effect estimates across DOPPS phases, and in the trend (e.g. a covariate that does not change over time cannot be a potential mediator in this analysis) in the mediator itself across phases. Alternative selections of mediators and confounders are presented in the supplemental materials. Sensitivity analyses were conducted using census data (with restricted covariate adjustment), sample data, different groups of practice measures, and different patient populations (e.g. age <65 v. 65+, male/female).

Results

Accelerated failure time models predict average life expectancy. The result of such a model on DOPPS dialysis patients, adjusting for age, is shown in Figure 2.3. The life expectancy in all three regions was either constant (Japan) or improving over time. Japan has consistently had the longest life expectancy.

Table 2.2 shows trends in the improved age-adjusted life expectancy per decade, derived from unadjusted and age-adjusted AFT models on survival within each region for census patients. Separate analyses of younger patients (<65 years of age), older patients (65+), males, and females are shown as well. Positive numbers in this table indicate increased average lifespan; e.g., the 1.45 for US age-adjusted trend over the course of the DOPPS study means that the lifespan increased by 45% per decade on average, or from under 4 years to approximately 6 years during this study.

Figure 2.4 shows the trends for each of these measures in the three regions. While some measures (e.g. phosphorous control, IDWG) show smooth, continuous improvement within each region, other measures (e.g. fistula use) show very different trends across the regions.

Age-adjusted survival has improved by 24% per decade in Europe, 9% per decade in Japan, and 45% per decade in the US (Table 2.22). These total survival improvements we observe could be described as consisting of two separate components: the direct effect and the indirect effect, as illustrated in figure 2.2. The indirect effect of the exposure (in this case,

calendar time) on the outcome (survival) is the extent to which these trends can be explained by the changes in the mediators (practice measures). [28] These indirect effects can be estimated through the product method; i.e. the effect of time on the practice measure times the effect of the practice measure on survival. The calculation and interpretation of the product-method estimates of the extent to which practice changes explain these trends can be illustrated using the changes in fistula use in the US (figure 2.4.a). In the US, case-mix-adjusted fistula use has increased an average of 30 percentage points per decade. In the model on patient survival, fistula use had a coefficient of 0.33, indicating that case-mix-adjusted survival for patients with fistulas was, on average, 1.39 (=exp(0.33)) times longer than for patients without fistulas. The product method calculation of the effect of fistula use on survival trends would thus be 30% of 0.33, or an indirect effect of 10%. This would mean that a 10% increase in patient lifespan per decade could be attributed to increased fistula use. The rest of the 45% improvement per decade in US patient survival would not be explained by the changes in fistula use; if fistula use were the only mediator considered, we would consider this remaining effect to be the direct effect of time on survival.

Figures 2.5.a-c show the results of using these methods to calculate the contribution of each practice measure, adjusting for the others, and combining the contributions. In Europe, the changes in practice measures explained a 12%(based on the sample, +/- 8%) or 17% (based on the facility census, +/- 6%) improvement in survival for the overall adult hemodialysis population (figure 2.5.a). The bootstrapped confidence intervals for the overall improvement in survival associated with these improvements in practice are not shown in the figure. In Japan, mediation by the practice measures explained a 9% (based on the sample, 95% confidence

interval +/- 6%) or 10% (based on the facility census, +/-4%) percent improvement in patient-mix-adjusted survival for the overall adult hemodialysis population (figure 2.5.b). In the US, the estimated improvement in survival mediated by these practices for the overall adult hemodialysis population was 26% (based on the sample, +/-9%) or 23% (based on the census, +/-6%) (figure 2.5.c).

One way to interpret of the results in Figures 2.5.a-c is as the proportional improvement per decade attributable to the change in the practice measure. For example, the European sample result sums to 12% (figure 2.5.a). Suppose two otherwise identical median European sample patients started dialysis in different time periods: one in 1999, and one in 2009. The one in 1999 would be expected to have a median lifespan of 4.4 years. If the only differences between the two patients were attributable to the changes in the practice measures, then the patient starting in 2009 would be expected to have a 12% longer lifespan, or 4.9 years. Similarly, a patient similar to the median sample patient (expected lifespan=12.4 years) in Japan in 1999 would be expected to have a lifespan of 13.5 (12.4*1.09) years in 2009 due to the 9% improvement in survival expected due to the changes in these practice measures. A median US sample patient with a lifespan of 3.1 years in 1999 would be expected to have a lifespan of 4.0 (3.1*1.26) years in 2009 due to the 26% improvement in expected survival resulting from the changes in these practice measures. These improvements are reasonably consistent across the different patient subgroups, including males, females, age <65 years, age 65 years and up, patients having less than a year on hemodialysis as of the start of follow-up within a phase (i.e. vintage < 1 year), and patients with a year or more on hemodialysis, as illustrated in supplemental figure 2.2.c. Across these various sensitivity analyses, these practice measures explain a 10-20% improvement per

decade in adjusted patient survival in Europe. In Japan they explain 5-15%, and in the US they explain 16-48% improvements in adjusted patient survival.

Using a similar interpretation, figure 2.5.a shows that improvements in Kt/V and phosphorous control in Europe can respectively explain 7% and 6% improvements in adjusted patient survival per phase. In Japan, improvements in Kt/V and IDWG can explain 3% and 4% improvements in adjusted patient survival per phase each (figure 2.5.b). The US results show that improvements in fistula use have been associated with a 10% improvement per decade in patient survival, while improvements in phosphorous control can explain a 7% improvement (figure 2.5.c). Alternative models based on the decrease in catheter use instead of the increase in fistula use in the US as the relevant measure of changes in vascular access practices showed similar results (supplemental figure 2.4.b versus supplemental figure 2.4.a).

Other potential mediators, including pre-dialysis systolic blood pressure, and PTH < 600 pg/ml, had mortality model effect estimates whose absolute value was 0.03 or less, and were dropped from this analysis.

Sensitivity analyses of different population subgroups generally showed consistent results within each region, although analyses of smaller subgroups or rarer outcomes (e.g. 1st-year mortality) tended to be more unstable with less precise estimates of effect. Supplemental Figure 2.6 shows the percentage of the overall mortality trend explained by each practice indicator for the identified subgroups, and sensitivity analyses. The wide confidence limits show that these

proportions can be very unstable when the confidence interval for the denominator (the overall trend in improved survival) approaches or overlaps zero.

Sensitivity analyses with and without the adjustment for residual urine volume in the sample-based analyses had very similar results (supplemental Figure 2.2.a-c). Results are shown with adjustment for residual urine volume. Figure 2.2.c shows that the relative contributions of different practice measures to improved survival tended to be consistent in subgroups of patients, including males, females, <65 years of age, and 65+ years of age. Factors that explained substantial improvements in survival overall tended to also explain substantial improvements in most patient subgroups. Analyses of patients who were included in the cross-section after less than a year on dialysis (vintage < 1 year) tended to be somewhat more unstable due to there being smaller numbers of these patients.

Figures 22.5a-c show the estimated indirect effects for the DOPPS sample of patients within the cross-sections at the beginnings of each phase within each region, as well as for the facility census of patients within this population. Most of the trends in practice measures have had positive effects on survival time; the trends running counter to improved survival (e.g. decreasing fistula use in Europe) tended to have smaller indirect effects on survival. The net effects in each region are positive in both models, indicating that this set of practices as a whole explains some of the improved adjusted survival time that has been seen over the phases.

It appears that fistula use consistently explains more of the improved survival in the US than is explained by the other factors, with Kt/V and phosphorous control contributing. In

Europe, the largest indirect effects were through Kt/V and phosphorous control. In Japan, the largest indirect effects were through Kt/V and IDWG.

The largest indirect effects shown in Figure 2.5 remain consistently larger when varying the list of mediating factors included in the analysis. Sensitivity analyses were conducted including the following practice measures: pre-dialysis systolic blood pressure 140-160 mmHg, ferritin 200-500 ng/ml, prescribed dialysate potassium level, prescribed dialysate sodium (at start, for sodium-modeled patients), dialysis session length, serum sodium level, and PTH < 600 pg/ml. The two factors whose mediated effects explained the most improvement in survival remained constant in each of the analyses with various subgroup analyses (including analyses using all practice measures), with the exception of hemoglobin. In Japan, hemoglobin 10-12 g/dl explained more of the improvement than either Kt/V or IDWG when included; however, this may have been due to the effect modification described below.

Practice measures whose effects varied substantially between DOPPS phases or regions were assumed to reflect factors other than biological associations between practice and outcome and were excluded from the final model used in the mediation analyses. For example, hemoglobin levels within the range of 10-12 g/dl had time-varying effects in the US and Japan. Regulatory and label changes for erythropoietin stimulating agents over the period studied prevented us from estimating the effects of adherence to a consistent practice guideline on outcomes over time, so hemoglobin 10-12 g/dl was excluded from the US and Japanese models. Other practices were excluded: PTH < 600 pg/dl (associated with improved survival in Europe and worse survival in Japan), dialysis session length (due to nearly non-overlapping session

lengths in the three regions), dialysate potassium (prior DOPPS research was unable to determine a universal recommendation[29]), and ferritin 200-500 ng/ml (mildly negative association with survival in Europe, mildly positive in Japan and the US).

Additional factors were left out of the final model because they either were in the causal pathway of another factor (e.g. DNa and serum sodium both affect IDWG), had ambiguous associations with mortality (dialysate potassium levels, blood pressure), had time-varying effects (e.g. hemoglobin in the US and Japan), or effects that were in opposite directions in different regions (e.g. PTH). The assumption was made that these variations indicated that we were not measuring true, unconfounded biological relationships with these practice measures.

Because residual urine volume might be considered both a pre-dialysis practice among nephrologists (e.g. initiating dialysis earlier v. later) as well as a during-dialysis practice among nephrologists (e.g. using diuretics to help retain urine output), we conducted sensitivity analyses excluding and including this covariate from the models. This had very little effect on the results (see supplemental figures 2, 4).

Discussion

The unadjusted life expectancy improved modestly in Europe and the US and decreased in Japan. Patient age has generally been increasing, and after adjusting for this, we can see that survival has improved within each of the three regions (Figure 2.3, Table 2.2). These improvements tend to be similar by sex and by age group (Table 2.2). This paper attempts to

explain the degree to which commonly-accepted practices may have contributed to this improvement in survival.

Facilities in Europe, Japan, and the US have, on average, seen improvements in several measures of dialysis practice , such as Kt/V, use of fistulas, hemoglobin control, phosphorous control, and IDWG (figures 4A-4E). For the sampled hemodialysis patient population, the improvements in practice would have explained a 12% per decade improvement in survival in Europe, 26% per decade survival in the US, and 9% per decade in Japan, depending on whether the census or sample data were used. In each region, these represent substantial proportions of the overall improvement in age-adjusted survival of 24%/decade in Europe, 51%/decade in the US, and 10%/decade in Japan. Sensitivity analyses using more or fewer practice indicators tended to show similar results in terms of the factors showing the largest indirect effects (i.e. largest ability to explain the mortality trends). The overall improvement in survival explained varied by age, sex, and time on dialysis from 10% - 20% in Europe, 5-15% in Japan, and 16-48% in the US.

Generally, the two most important factors in each region consistently explained substantial contributions towards increased lifespan among hemodialysis patients across these demographic groups within both the census and the sample (Figures 2.5.a-c, Supplemental Figure 2.2.c). These factors explaining substantial amounts of the improved survival included: fistula use and phosphorous control in the U.S.; Kt/V and serum phosphorous control in Europe; and Kt/V and IDWG in Japan.

Caveats and limitations

An assumption made in these analyses is that changes in practices affect patient survival in a causal manner. There are substantial a priori reasons for believing a causal relationship between each of these measures and patient outcomes, as suggested by the fact that several professional organizations have recommendations for these practice areas based on research and expert opinion. The associations between these factors and patient mortality have been replicated in multiple independent analyses. However, since the current and prior analyses were generally based on observational data, we cannot rule out confounding from other factors such as improvements in patient behavior, other treatments, or changes in the patient population outside the demographic and comorbid data collected.

Each of the treatment measures may reflect factors other than treatment. For example, Kt/V is influenced by patient willingness to stay throughout the entire prescribed dialysis session. IDWG can be influenced by patient dietary habits as well as prescribed dialysate sodium levels and physician estimates of patient dry weight. Phosphorous levels can be influenced by diet and phosphate binder prescription adherence. Thus, the changes in the covariates labeled 'practice measures' may also reflect trends in patient behavior.

There may also have been improvements in factors outside of the dialysis treatment-specific factors explored in this paper that have resulted in improving dialysis patient survival. For example, the primary identified causes of death among dialysis patients are cardiovascular disease.[30] General improvements in cardiac care or reductions in smoking could have resulted in improved dialysis patient survival over this period, and this improvement may not have

necessarily been in any way related to the improved markers of dialysis patient care used in these analyses.

One potential criticism of this analysis using observational data is that the practice measures we have chosen may represent general indicators of facilities with practices that are generally of high quality, instead of the direct effect of the specific measure. We analyzed facility-level correlations of the five practice measures used in the final analyses in this manuscript. If these measures reflect facilities with generally high-quality practice, we would expect these measures to be highly correlated; the result we found, controlling for country and phase, was that these correlations were generally low; mostly between -0.10 and 0.10. This evidence suggests that these practices are somewhat independent of each other, indicating that facilities do not have strong tendencies towards being high quality in all areas or low quality practices in all areas. See supplemental materials for more detail.

The patient population may have changed in ways that are not completely captured in the demographics and comorbid factors analyzed. One possibility might include increased prevalence over time of dialysis patients with residual renal function. Residual renal function is associated with better survival among dialysis patients.[31,32] Patients were put on dialysis earlier, as measured by the estimated glomerular filtration rate (eGFR) at the start of dialysis, from 1996 through 2010, with evidence that this trend had leveled off after 2010.[33] This would imply that patients enrolled in the later periods would tend to retain more of their residual renal function. To the extent that this trend was not captured via our inclusion of daily urine volume <200 mL v. 200+ mL, this could have confounded the analysis.

Sampling in the US in phases 4 and 5 was complicated by the inclusion of facilities where primary data collection was through electronic health records (EHR), the results of which were adapted to the DOPPS data collection fields. Adjustment was handled using an indicator for EHR data collection in the US during these phases, which would not be adequate for changes in the effects of covariates (e.g. comorbidities). This issue would only affect the US trends.

Conclusions

To our knowledge, the reasons for the improving trend in age-adjusted dialysis patient survival seen in four European countries (24%/decade), the US (51%/decade), and in Japan (10%/decade) since 1999 have not been adequately addressed in the literature. A substantial proportion (>50%) of these improving trends can be explained through improvements in dialysis practice. For the entire hemodialysis patient population, the improvements in practice would have explained a 12-17%/decade improvement in survival in Europe, 23-26%/decade survival in the US, and 8-10%/decade in Japan. In each region, these represent substantial proportions of the overall improvement. While there is variation between the amount of improvement explained for specific groups of patients (by age, sex, or time on dialysis), all of these estimates were positive. In the European countries, fewer patients with Kt/V < 1.2 and improved phosphorous control can explain some of the improvement. In Japan, improvements in Kt/V and IDWG can explain some of the improvement. In the US, improvements in fistula use and phosphorous control can explain some of the improvement. These results are consistent across analyses based on varying datasets, levels of adjustment, and the inclusion or exclusion of other potential mediators. These improvements in these practice measures are likely to have been substantial reasons behind the

trends in improved survival among dialysis patients since 1999. In order to continue to improve dialysis patient survival, it seems likely that we will have to continue to both investigate ways to improve current recommendations and to increase adherence to these practice recommendations.

Tables and figures

Table 2.1: Summary statistics (count, mean, or %) of outcomes, demographics, comorbid conditions, and practice measures, by DOPPS phase and by region

	DOPPS Phase (years)					Region		
	1 (99-01)	2 (02-04)	3 (05-08)	4 (09-11)	5 (12-15)	Europe	Japan	US
Patients, events, and follow-up								
Census count	19931	15750	15700	19345	17432	26264	27121	34773
DOPPS sample size	7115	5667	5483	6830	5956	10094	8523	12434
No. Deaths (sample)	1664	1307	1253	1466	1362	2513	979	3560
Average follow-up (years)	1.6	1.6	2.0	1.7	1.9	1.8	2.1	1.5
Demographics and comorbid factors in sample								
Age	60.2	61.8	62.5	64.3	65.0	63.6	62.2	62.3
Age 65+ (%)	42%	48%	49%	53%	55%	55%	44%	48%
Body mass index	23.8	24.2	24.5	26.0	25.8	25.2	20.9	27.4
Coronary artery disease	35%	44%	54%	38%	30%	38%	28%	49%
Cancer	8%	10%	12%	12%	12%	13%	8%	11%
Cardiovascular, other	30%	34%	35%	28%	22%	34%	28%	27%
Cerebrovascular	15%	16%	16%	14%	12%	16%	13%	15%
Congestive heart failure	29%	28%	37%	28%	22%	24%	16%	41%
Diabetes	35%	36%	38%	47%	46%	28%	32%	57%
Gastro-intestinal bleed	6%	6%	5%	5%	4%	5%	4%	6%
Hypertension	74%	77%	80%	82%	84%	79%	70%	86%
Lung disease	9%	10%	11%	13%	10%	13%	3%	14%
Neurologic disease	7%	11%	11%	11%	8%	10%	7%	11%
Psych disorder	18%	18%	12%	17%	13%	18%	4%	22%
Peripheral vascular disease	20%	24%	26%	26%	20%	27%	14%	26%
Recurring cellulitis	6%	7%	7%	10%	6%	8%	4%	10%
Vintage	5.1	4.9	5.6	5.3	5.5	5.0	7.9	3.7
Residual urine volume >200 ml/day	25%	26%	30%	26%	26%	33%	22%	24%
Practice Measures								
% Kt/V 1.2+ (fac avg)	75%	77%	82%	86%	87%	79%	74%	88%
% Fistula (fac avg)	53%	61%	71%	65%	72%	72%	91%	40%
% catheter (fac avg)	26%	23%	16%	24%	18%	22%	2%	35%
% Albumin 4+g/dl (fac avg)	35%	33%	37%	36%	33%	38%	30%	36%
% Hgb 10-12 g/dl (fac avg)	47%	46%	48%	57%	61%	48%	52%	54%
%IDWG <5.7% (fac avg)	87%	89%	91%	93%	95%	95%	85%	91%
% Phosph < 6 Mg/dl (fac avg)	60%	63%	70%	74%	75%	72%	66%	67%
% Hgb 10+g/dl	68%	77%	83%	84%	80%	84%	61%	85%
% Phosph 4-6 Mg/dl (fac avg)	45%	47%	51%	53%	54%	48%	53%	49%
% Ferritin 200-500 ng/ml (fac avg)	29%	32%	32%	27%	23%	37%	19%	28%
% Post-dialysis SBP 140-160 mmHg (fac avg)	30%	29%	25%	25%	26%	24%	33%	26%
% Pre-dialysis SBP 140-160 mmHg (fac avg)	37%	36%	34%	33%	34%	33%	39%	33%
Avg pts/nurse	4.5	6.9	7.9	6.7	6.7	6.2	5.8	7.3

	DOPPS Phase (years)					Region		
	1 (99-01)	2 (02-04)	3 (05-08)	4 (09-11)	5 (12-15)	Europe	Japan	US
Avg. pts/non-nurse staff	6.6	9.1	8.0	7.5	8.2	5.9	14.0	4.0
Prescribed dialysate potassium (mEq/l)	2.1	2.0	2.1	2.1	2.2	2.1	2.0	2.1
Prescribed dialysate sodium at start	140.8	140.9	140.2	139.2	139.4	139.4	140.6	140.5
Treatment time	227.3	229.4	233.6	228.6	231.9	236.4	239.8	218.0
Serum sodium mEql	138.3	138.3	138.4	138.2	138.1	138.2	138.9	137.9
PTH < 600 pg/ml (fac avg)	88%	90%	89%	89%	88%	88%	95%	85%

Fac avg: average calculated from DOPPS sample patient data within the facility, if the facility had at least 10 such patients with non-missing data. All demographic, comorbid factors, and practice measures listed have a p-value < 0.0001 for their trend over time within at least one region with the sole exception of HIV. Comorbid conditions, BMI, and practice measures expressed as percentages are all based on 31,080 sampled patients.

Table 2.2: Average proportionate improvement in expected lifespans per decade; unadjusted and adjusted for age, by age and sex within each region

	Unadjusted			Age Adjusted		
	US	Europe	Japan	US	Europe	Japan
All	1.33 (1.27 - 1.41)	1.02 (0.97 - 1.08)	0.82 (0.76 - 0.89)	1.45 (1.38 - 1.53)	1.24 (1.17 - 1.31)	1.09 (1.01 - 1.18)
<65	1.33 (1.27 - 1.41)	1.02 (0.97 - 1.08)	0.82 (0.76 - 0.89)	1.45 (1.38 - 1.53)	1.24 (1.17 - 1.31)	1.09 (1.01 - 1.18)
65+	1.37 (1.26 - 1.5)	1.2 (1.08 - 1.34)	0.99 (0.86 - 1.15)	1.47 (1.35 - 1.6)	1.24 (1.11 - 1.38)	1.13 (0.98 - 1.3)
Female	1.35 (1.26 - 1.44)	1.1 (1.03 - 1.17)	0.98 (0.9 - 1.08)	1.46 (1.37 - 1.56)	1.25 (1.17 - 1.33)	1.07 (0.97 - 1.17)
Male	1.35 (1.26 - 1.44)	1.1 (1.03 - 1.17)	0.98 (0.9 - 1.08)	1.46 (1.37 - 1.56)	1.25 (1.17 - 1.33)	1.07 (0.97 - 1.17)

Legend: Estimates from phase as a continuous predictor of survival in AFT models on 88,253 DOPPS Census patients within each region, limited to the specified demographic listed.

Table 2.3: Mediation analysis results: components (separate model estimates) and product estimate of indirect effect through each practice measure, within the sample patients and for the census patients, by region

		US		Europe		Japan	
		Sample	Census	Sample	Census	Sample	Census
Product estimate of indirect effect of phase and practice measure / decade	Kt/V 1.2+	0.048 (0.029, 0.069)	0.024 (0.012, 0.036)	0.071 (0.039, 0.102)	0.06 (0.035, 0.082)	0.031 (0.015, 0.048)	0.058 (0.042, 0.075)
	IDWG < 5.7%	0.015 (-0.006, 0.033)	0.029 (0.009, 0.046)	-0.011 (-0.059, 0.032)	0.001 (-0.03, 0.034)	0.041 (0.01, 0.074)	0.039 (0.012, 0.067)
	Fistula (proportion)	0.099 (0.022, 0.183)	0.093 (0.042, 0.14)	-0.011 (-0.02, -0.004)	-0.01 (-0.016, -0.004)	0.004 (-0.007, 0.018)	0.01 (0.005, 0.018)
	Phosphorous < 6 mg/dl	0.07 (0.034, 0.107)	0.056 (0.031, 0.083)	0.057 (0.022, 0.098)	0.066 (0.041, 0.097)	0.007 (-0.035, 0.041)	-0.014 (-0.033, 0.008)
	Hgb 10-12 g/dl	N/A	N/A	0.011 (-0.025, 0.056)	0.039 (0.011, 0.069)	N/A	N/A
Beta of mediator in model on survival	Kt/V 1.2+	1.118 (0.665, 1.543)	0.584 (0.3, 0.91)	0.594 (0.329, 0.889)	0.498 (0.293, 0.671)	1.029 (0.511, 1.509)	1.049 (0.765, 1.329)
	IDWG < 5.7%	0.313 (-0.12, 0.697)	0.496 (0.15, 0.76)	-0.201 (-1.073, 0.585)	0.015 (-0.494, 0.573)	0.743 (0.19, 1.392)	0.495 (0.158, 0.854)
	Fistula (proportion)	0.331 (0.073, 0.626)	0.324 (0.145, 0.486)	0.776 (0.458, 1.001)	1.041 (0.826, 1.239)	0.257 (-0.383, 1.023)	0.667 (0.353, 1.022)
	Phosphorous < 6 mg/dl	0.792 (0.386, 1.183)	0.597 (0.327, 0.87)	0.48 (0.179, 0.818)	0.571 (0.357, 0.828)	0.098 (-0.54, 0.632)	-0.234 (-0.563, 0.143)
	Hgb 10-12 g/dl	N/A	N/A	0.128 (-0.29, 0.64)	0.430 (0.119, 0.774)	N/A	N/A
Beta, scaled to show effect of decade, in model on mediator	Kt/V 1.2+	0.044 (0.04, 0.047)	0.04 (0.038, 0.042)	0.118 (0.11, 0.126)	0.121 (0.115, 0.125)	0.031 (0.024, 0.039)	0.056 (0.052, 0.06)
	IDWG < 5.7%	0.048 (0.044, 0.052)	0.059 (0.057, 0.062)	0.055 (0.052, 0.058)	0.061 (0.059, 0.063)	0.055 (0.049, 0.061)	0.079 (0.076, 0.082)
	Fistula (proportion)	0.297 (0.289, 0.305)	0.287 (0.283, 0.292)	-0.015 (-0.024, -0.006)	-0.01 (-0.014, -0.004)	0.018 (0.014, 0.022)	0.016 (0.013, 0.018)
	Phosphorous < 6 mg/dl	0.089 (0.083, 0.095)	0.094 (0.091, 0.097)	0.119 (0.112, 0.126)	0.116 (0.112, 0.12)	0.065 (0.059, 0.072)	0.059 (0.056, 0.062)

		US		Europe		Japan	
		Sample	Census	Sample	Census	Sample	Census
	Hgb 10-12 g/dl	N/A	N/A	0.086 (0.082, 0.091)	0.091 (0.088, 0.094)	N/A	N/A
Overall	Direct effect	0.105 (-0.026, 0.241)	0.121 (0.037, 0.192)	-0.032 (-0.157, 0.077)	0.064 (-0.007, 0.142)	-0.035 (-0.189, 0.118)	-0.057 (-0.144, 0.044)
	Total effect	0.401 (0.313, 0.503)	0.364 (0.311, 0.416)	0.102 (0.005, 0.189)	0.215 (0.169, 0.279)	0.12 (-0.03, 0.255)	0.086 (0.018, 0.169)

Legend: Product-method mediation analysis results using linear models for the first stage (mediator versus phase), and a gamma AFT model for the second stage (survival versus mediator). All potential mediators in each region were considered together in the same AFT model, and each separate linear model on each mediator included the other mediators as predictors. Analyses adjusted for age, race, sex, vintage, and EHR identifier in the census-based models, or all of those variables plus 13 comorbid conditions and BMI in the sample-based models. Results are the 2.5^{th}, 50^{th}, and 97.5^{th} percentiles from a bootstrap analysis with 200 iterations.

Figure 2.1: Inclusion criteria and sample size

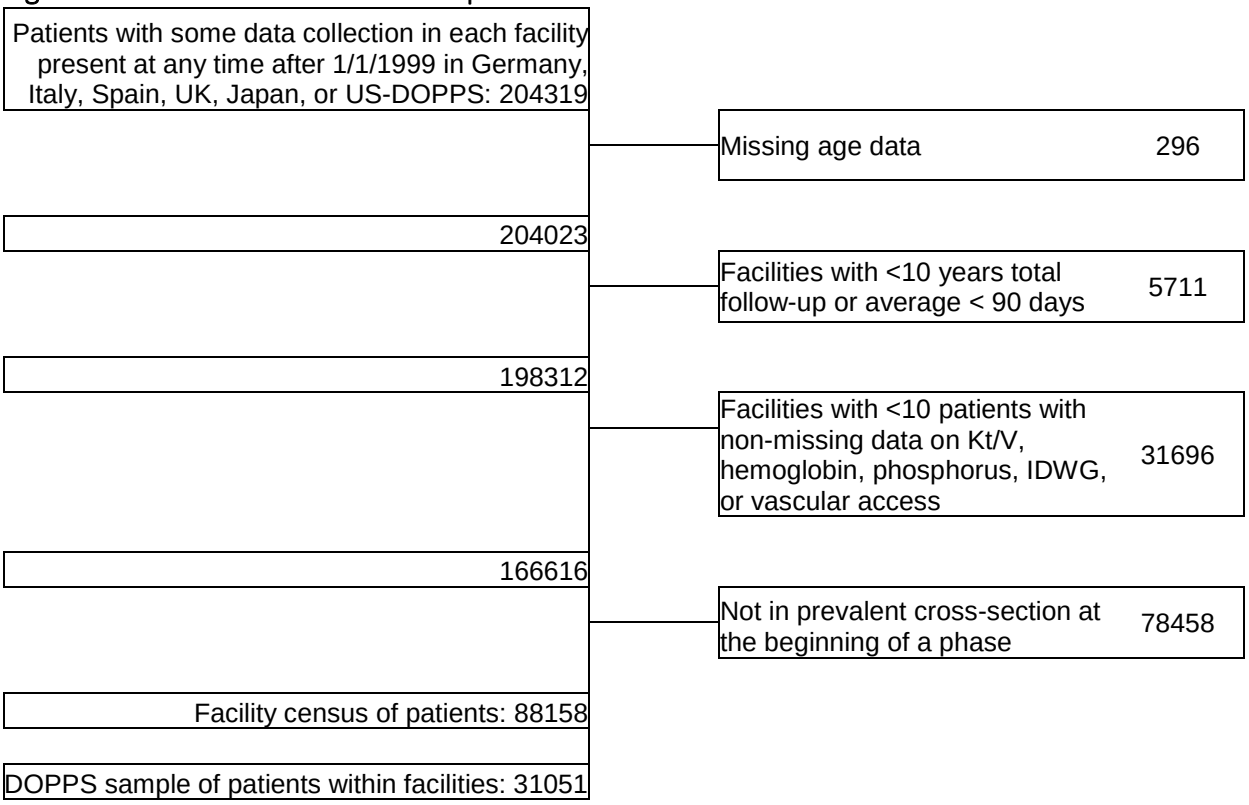
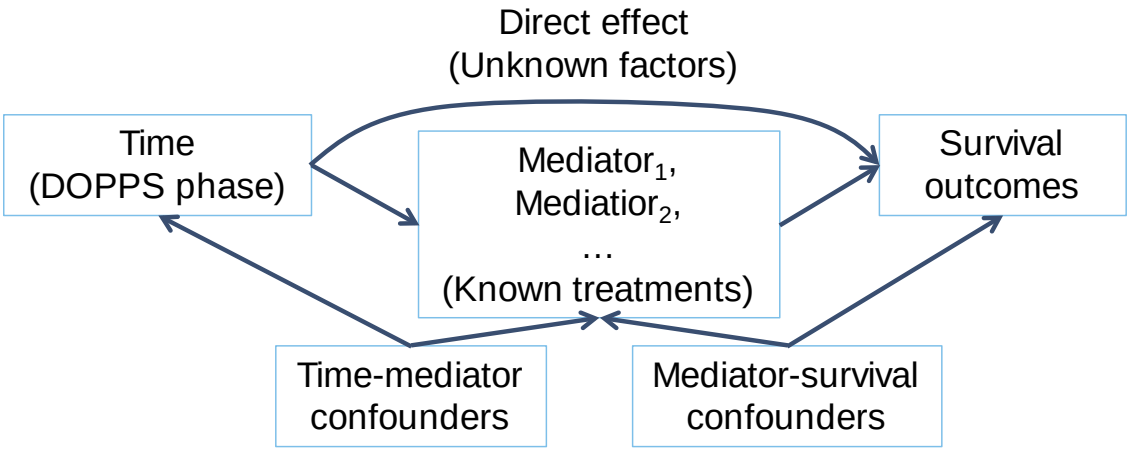


Figure 2.2 Causal diagram Illustrating the mediation analysis



Legend: The total effect of time on survival can be split into an indirect effect, operating through changes in practice measures, and a direct effect, operating independently of the practice measures. Each of these relationships might have confounders, and these confounders might have different effects on different associations.

The equations would thus be:

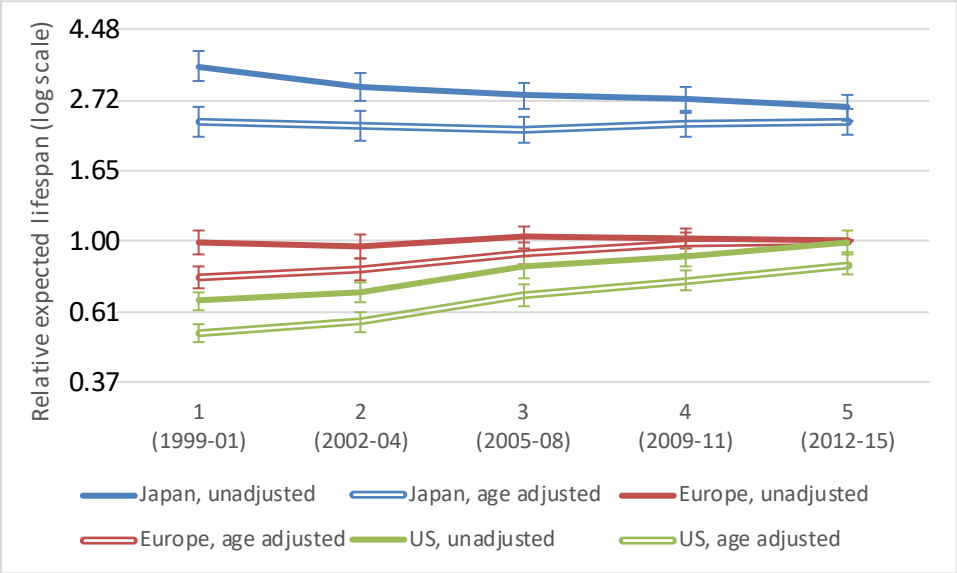
$Mediator_p = \theta_0 + \theta_p Time + \theta(\text{Time-mediator confounders}) + \theta\ (\text{other mediators})$

Survival time $T = \Gamma(\delta^{-2}, \delta^{-2} \exp(\beta_0 + \beta_1(mediator_1) + \beta_2\ (mediator_2) + \ldots + \beta_p(mediator_p) + \beta\ (\text{mediator-survival confounders}))/\ \Gamma(\delta^{-2})$

Where Γ is the incomplete gamma function and δ is a free shape parameter.[34]

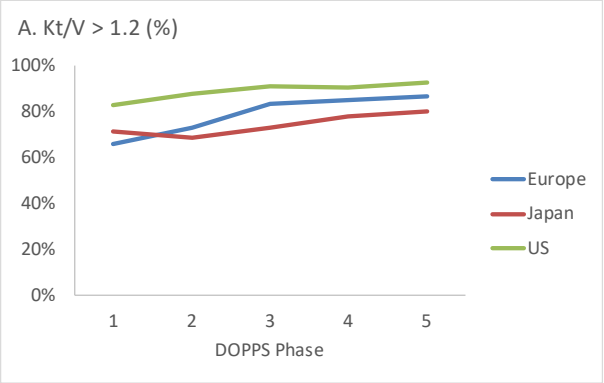
With this formulation, the product-method estimate for the indirect effect of time through mediator p on survival, controlling for confounding and other mediators, is $\theta_p\beta_1$.

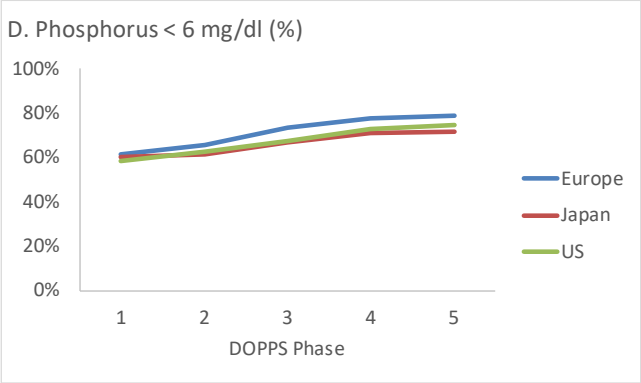
Figure 2.3. Relative expected lifespan, proportional to Europe phase 5, for ratios by region and DOPPS phase, unadjusted and adjusted for age

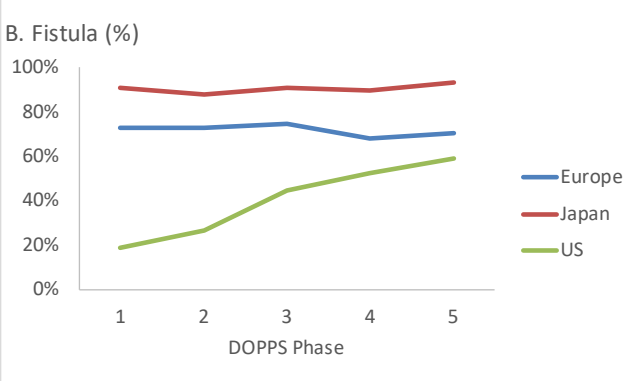


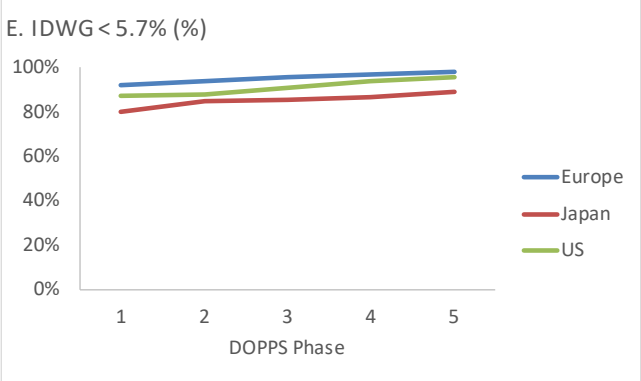
Footnote: Reference = phase 5 Europe within both the census and the sample plots. Relative expected lifespans are based on an AFT model, unadjusted and adjusting for patient age at baseline. Census data is complete census for facilities, including EHR data, excluding patients with missing age and US patients who left the DOPPS study prior to 1999. N = 88,253

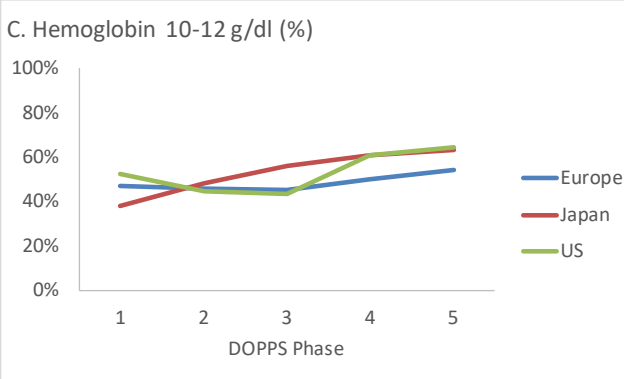
Figure 2.4 a-e: Trends in treatment measure prevalence across DOPPS phases by region. A: Kt/V > 1.2. B: Fistula use, C: Hemoglobin 10-12 g/dl, D: Phosphorous < 6 mg/dl, E: IDWG < 5.7%.











Legend: Figures 2.4 A-E show the average of each practice measure across the five DOPPS phases (1: 1999-2001, 2: 2002-04, 3: 2005-08, 4: 2009-11, 5: 2012-15).

Figures 2.5.a-c: Positive, negative, and net indirect effects of DOPPS phase (1-5) on improvement in patient survival, mediated by changes in facility practices, in the DOPPS sample and census, by region: a. Europe, b. Japan, c. US.

2.5.a: Europe

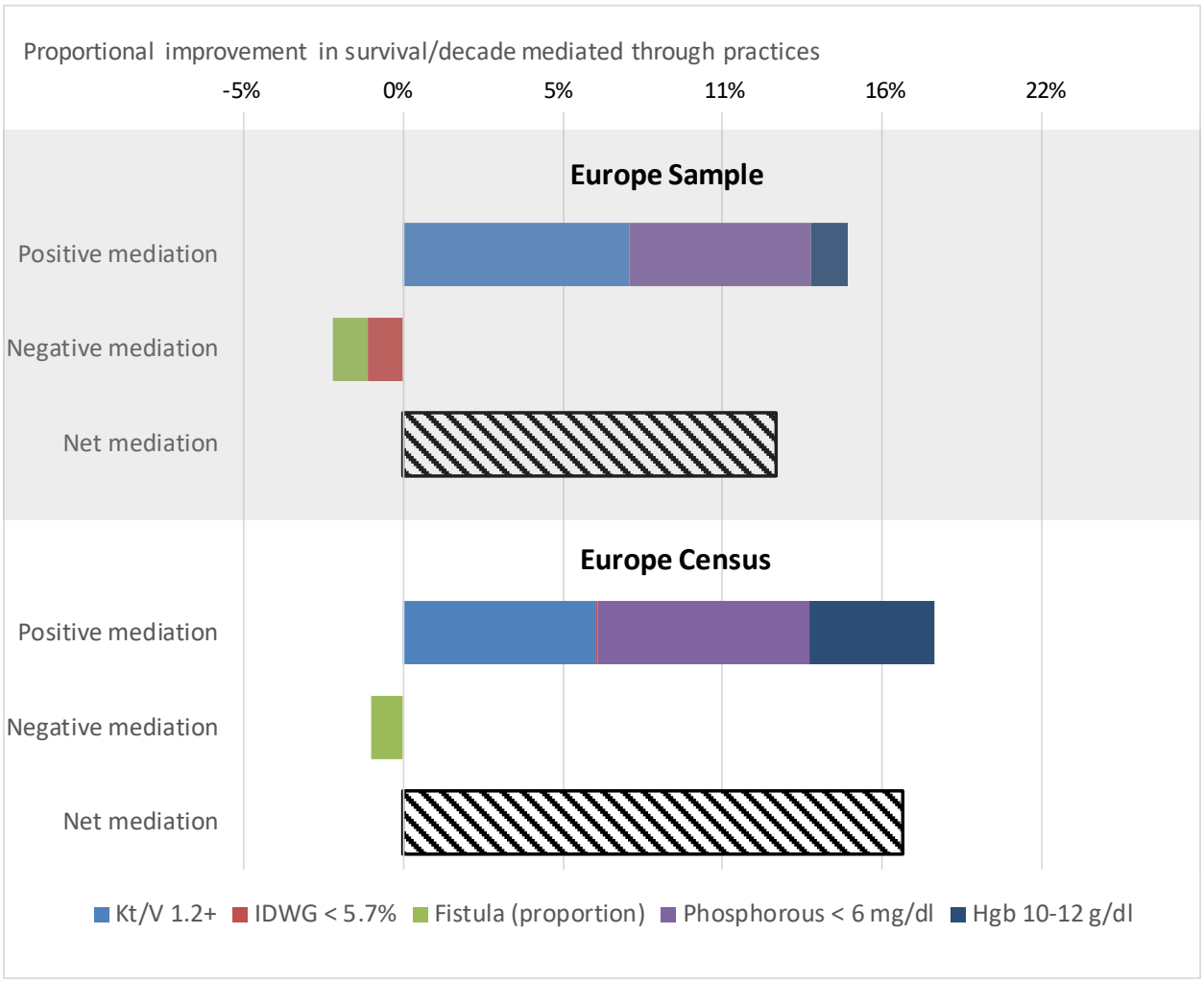


Figure 2.5.b: Japan

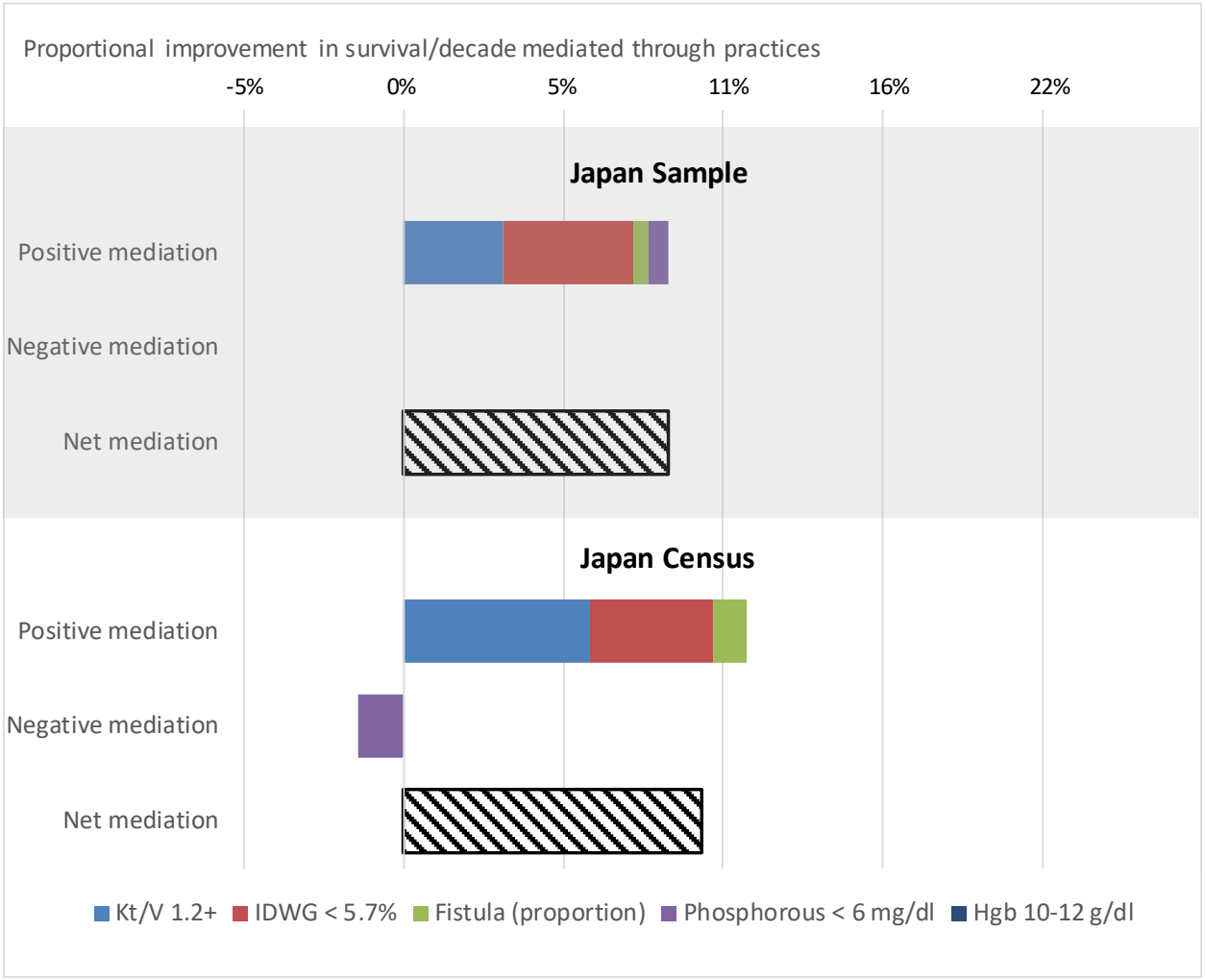
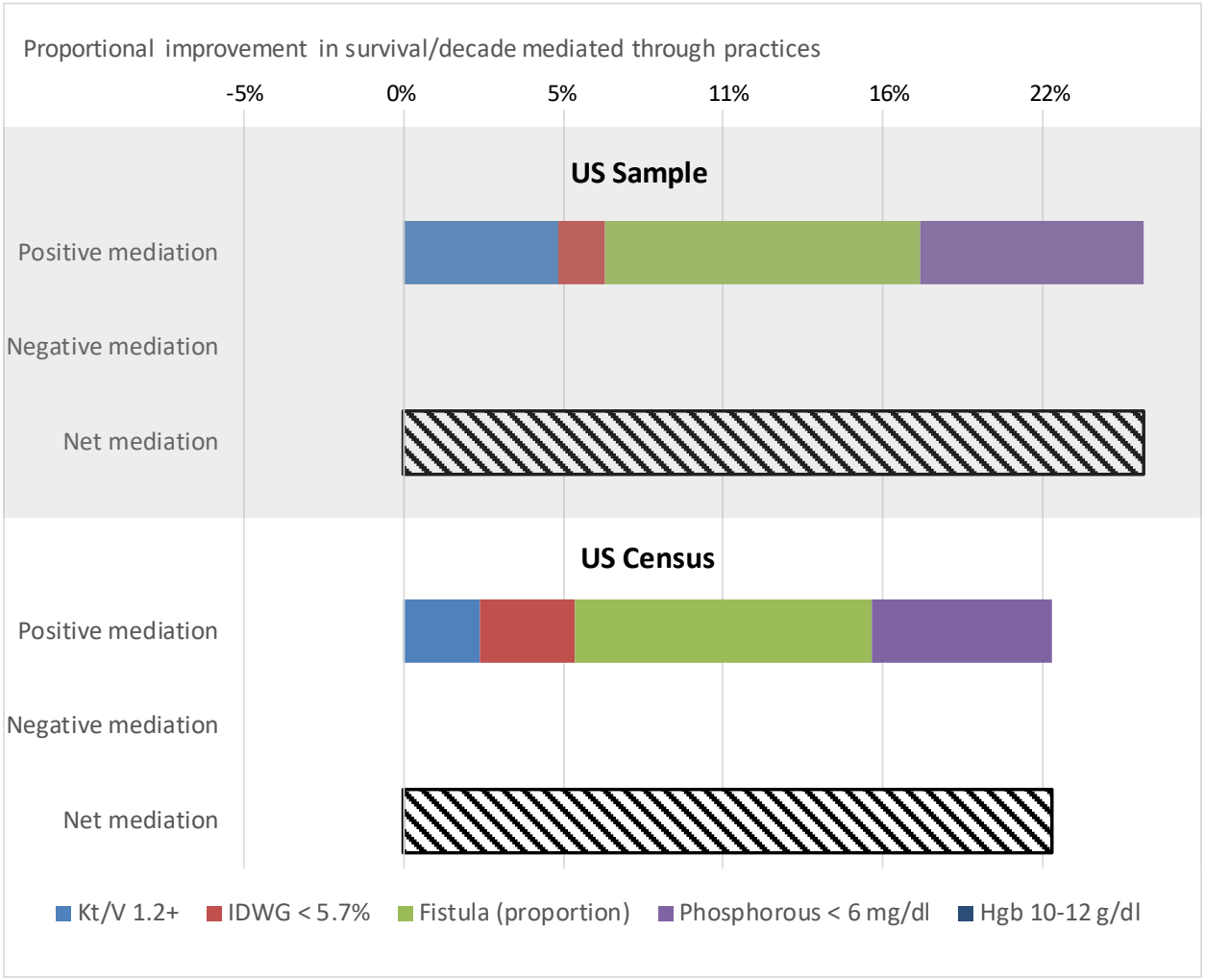


Figure 2.5.c: US

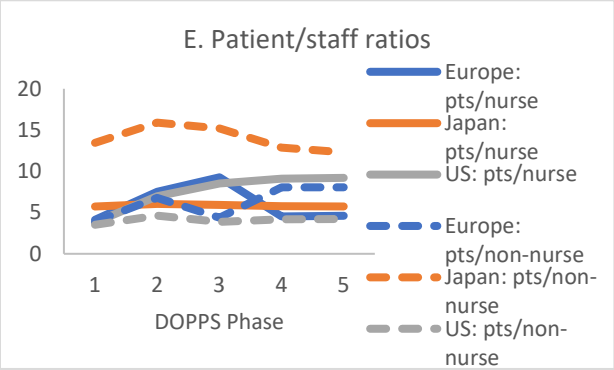


Legend: Each indirect effect is estimated as the proportional improvement in expected survival time that occurred due to changes in these practice measures. The results have been normalized to show the effect per decade that was mediated by these practice measures. Positive mediation is where changes in certain mediators result in more improvement in survival (partly explaining the time trend), and negative mediation is where changes in other mediators result in less improvement in survival. The net effect is the net mediated change in mortality per phase over the period between phase 1 (1999-2001) and phase 5 (2012-2015); i.e. the sum of the positive and negative mediating effects within that model on a log scale.

All potential mediators in each region were considered together in the same AFT model, and each separate linear model on each mediator included the other mediators as predictors. Analyses adjusted for age, race, sex, vintage, and EHR identifier in the census-based models, or all of those variables plus 13 comorbid conditions and BMI in the sample-based models.

Supplemental materials

Supplemental Figure 2.1 Trends in staffing ratios by region

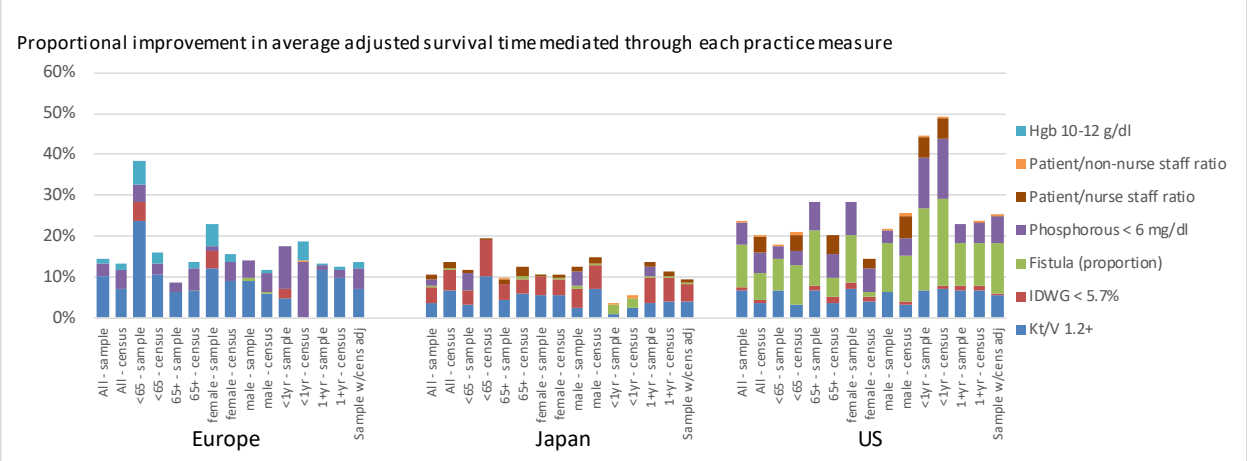


Legend:

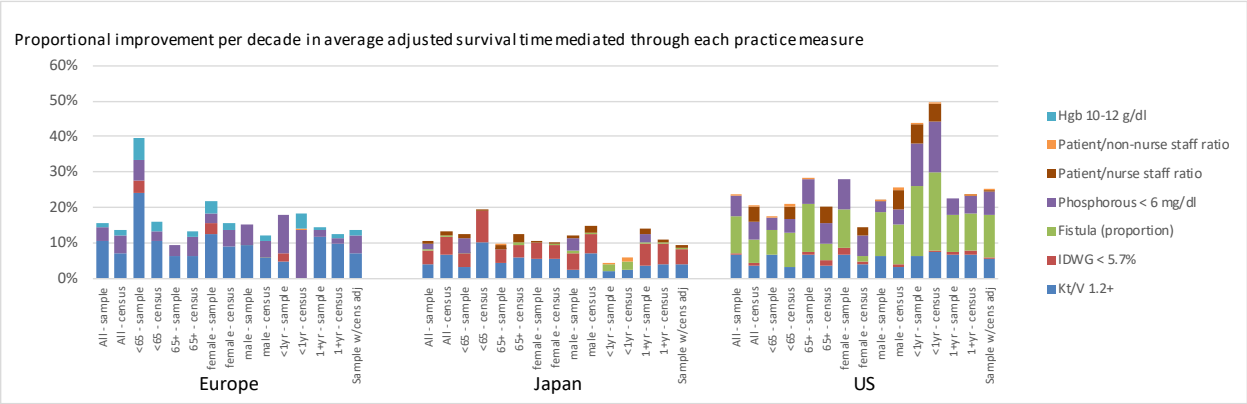
Graphs show trends in the average of these staffing ratios across the five DOPPS phases (1999-2001, 2002-04, 2005-08, 2009-11, 2012-15).

Supplemental Figure 2.2.a-c: Comparison of results of product method estimates of indirect effects per decade mediated through practice measures across sample and census patient populations by age, sex, and dialysis vintage a) without adjusting for residual renal function and including staffing ratios, b) adjusting for residual renal function and including staffing ratios, and c) adjusting for residual renal function and excluding staffing ratios.

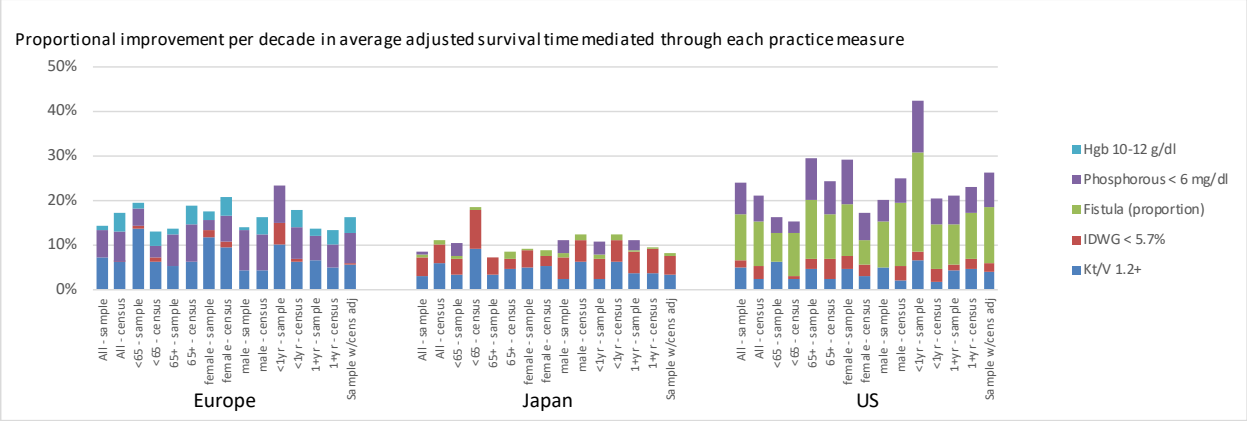
2.2.a Without adjusting for residual urine volume, including staffing ratios



2.2.b Adjusting for residual urine volume, including staffing ratios



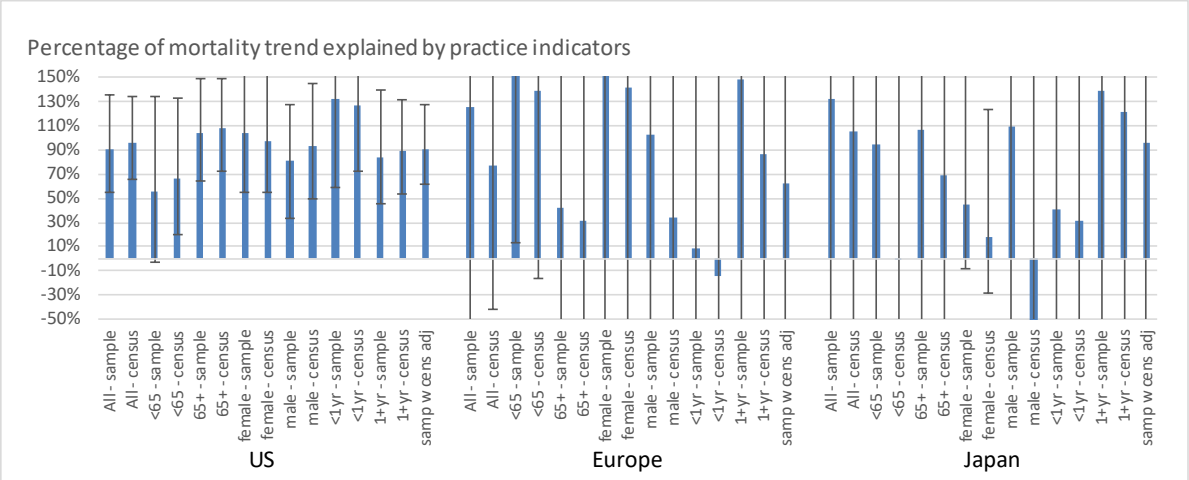
2.2.c Adjusting for residual urine volume, excluding staffing ratios



Legend: Results include product-method estimates of indirect effects of time on survival mediated through each individual practices, separately for each region, and separately for the sample and for the full census within each region, also for sub-populations: age (<65, 65+), sex, time on dialysis at start of study (< 1 year, 1+ years), and for the sampled patients but limiting adjustment to the factors available on the census. These plots show the consistency in the results between patient subgroups, but for simplicity, the smaller negative mediating effects were omitted. If these results were included, then the range of the overall effect of these contributions between subgroup analyses would have been 10-20% in Europe instead of the 14-25% shown in the graph, 5-15% in Japan instead of the 7-19% shown in the graph, and the range of the US sums would be unchanged at 16-48%.

The mediators in each region were considered together in each of the models, which also were adjusted for age, race, sex, vintage, and EHR identifier in the census-based models, or all of those variables plus 13 comorbid conditions and BMI in the sample-based models. Japan models on patients with <1 year of dialysis were excluded because they frequently had convergence problems, being based on 95 deaths in the sample. The results including staffing ratios, which had very weak associations (<0.03 per additional patient/staff) with expected mortality rates using the models in this paper, were included in figures A and B. Residual urine volume was measured as reported volume at baseline <200 ml/day versus 200+ ml/day. The largest difference between models with and without residual urine volume is in the effect of phosphorous <6 mg/dl in Europe in mortality models using sampled patients under the age of 65, which went from 0.014 (without adjustment for residual urine volume) to 0.018 (with adjustment for residual urine volume); most differences were <0.001.

Supplemental Figure 2.3: Percentage of mortality trend explained[35] by practice indicators (including staffing ratios), by region (US, Europe, Japan), for sample patients and for census patients within each region, by category: age (<65 v. 65+), sex (male v. female), vintage (<1 year v. 1+ year), and for sample patients using census adjustment factors

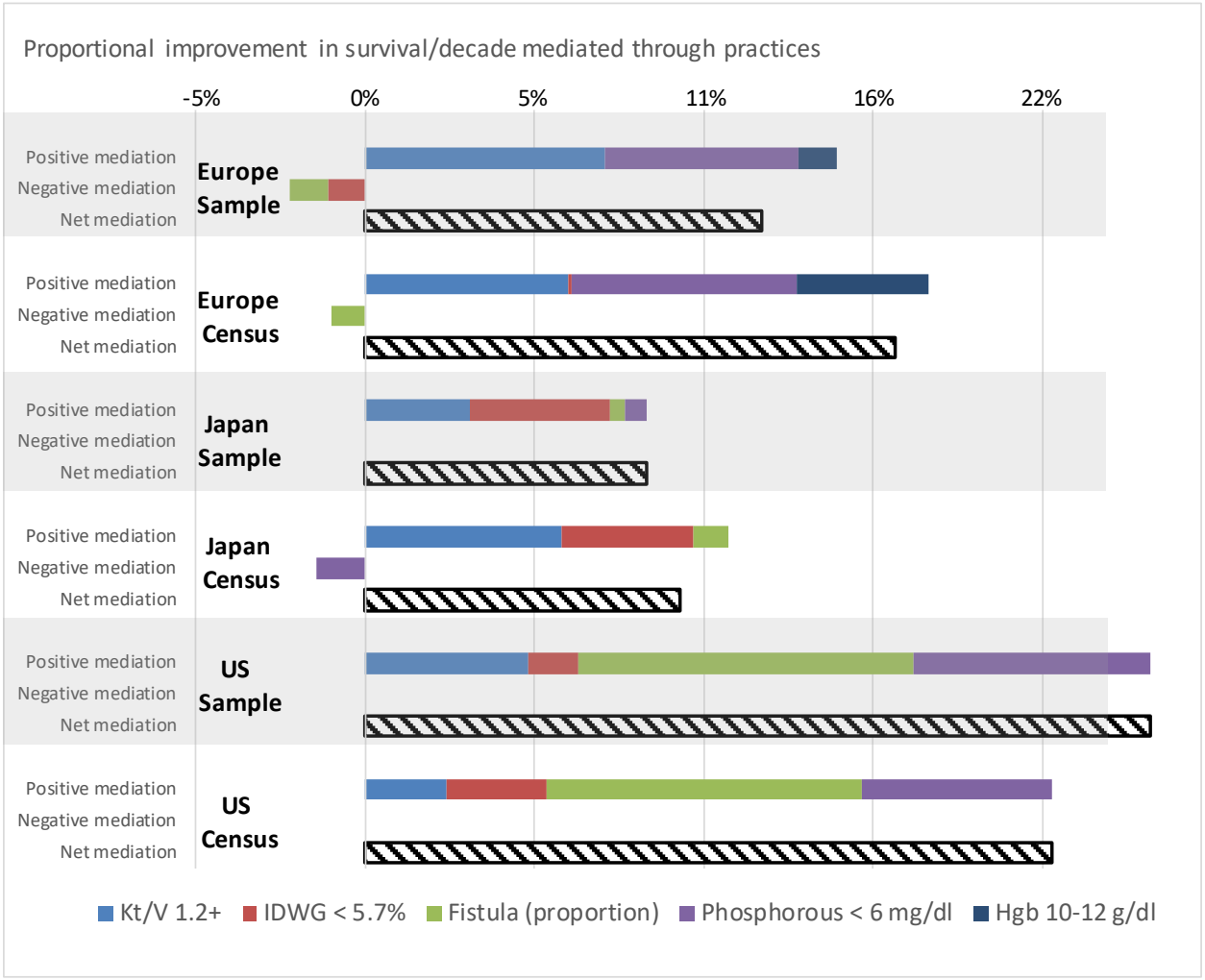


Legend:

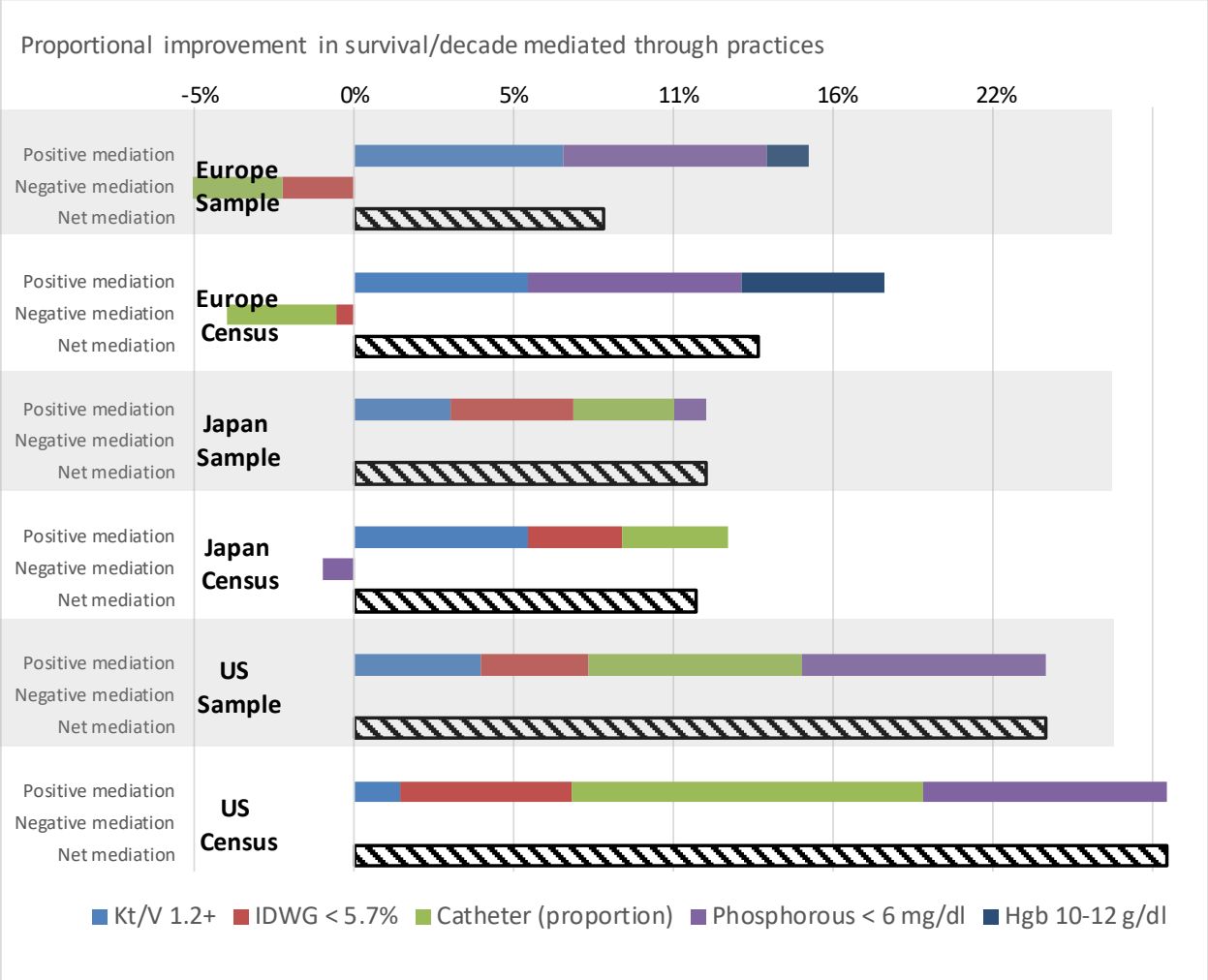
Bootstrapped results (200 iterations) for confidence ranges (2.5th percentile – 97.5th percentile).
"Sample" = DOPPS sample patients, adjusted for demographics and comorbid conditions.
"Census" = Full DOPPS census, adjusted only for vintage, age, black/non-black, EHR status (US), and sex.
"All" = No additional filters on age or vintage
"<65" = only patients aged <65 at the beginning of follow-up
"65+" = only patients aged 65+ at the beginning of follow-up
"<1yr" = only patients with less than one year of dialysis (vintage <1) at the beginning of follow-up
"1+yr" = only patients with more than one year of dialysis (vintage 1+) at the beginning of follow-up
"samp w cens adj" = using sample patients only, but restricting the adjustments to those used in the census
See Table 2.1 for counts of patients used in each model (sample and census, within each region)

Supplemental Figures 2.4a-b: Positive, negative, and net indirect effects* of DOPPS phase (1-5) on improvement in patient survival, mediated by changes in facility practices, in the DOPPS sample and census, by region and adjusting for residual renal function while excluding staffing ratios. a. Based on fistula use as a measure of vascular access practice changes b. Based on catheter use as a measure of vascular access practice changes

2.4.a Based on fistula use as a measure of vascular access practice changes



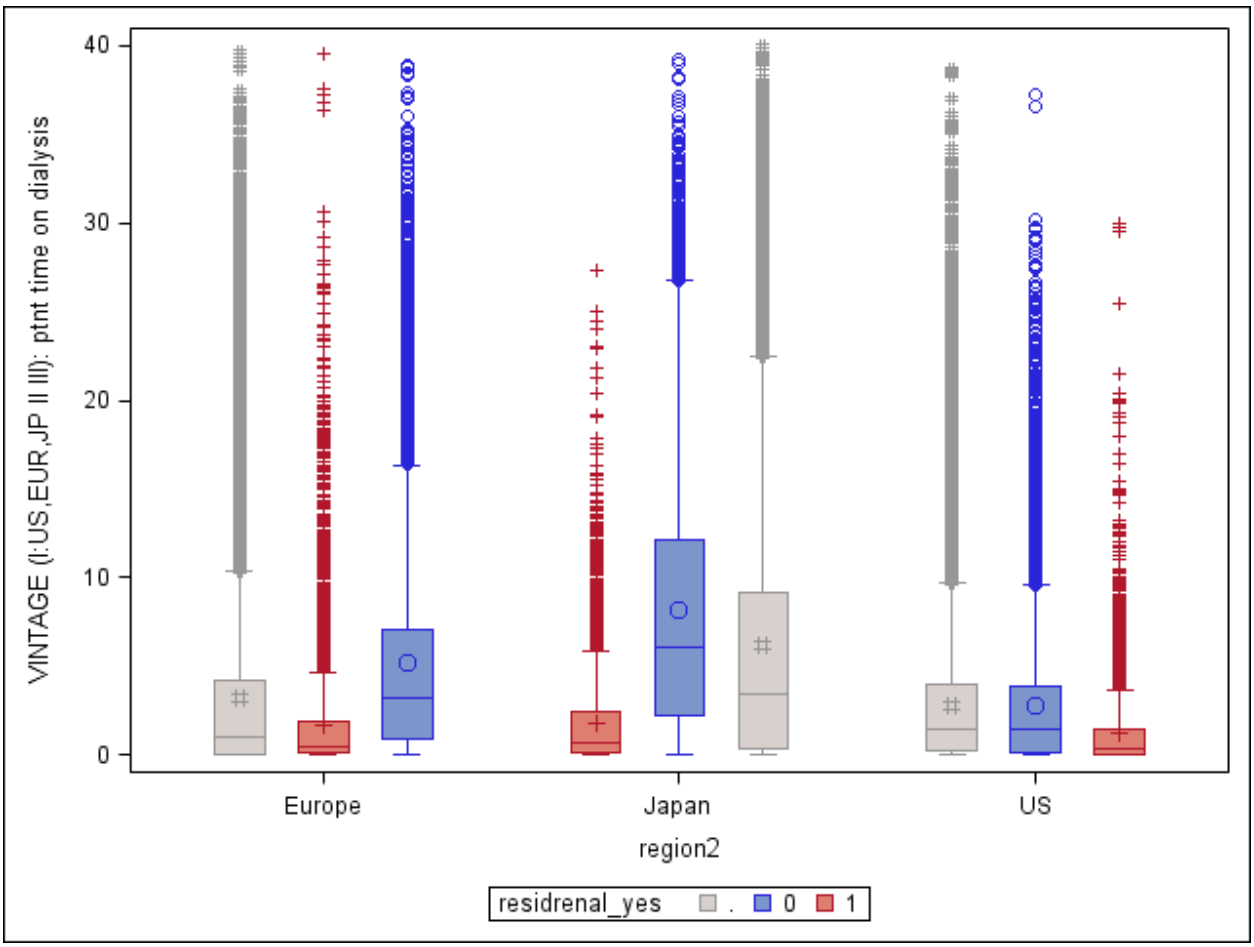
2.4.b Based on catheter use as a measure of vascular access practice changes



Legend: Each indirect effect is estimated as the proportional improvement in expected survival time that occurred due to changes in these practice measures. The results have been normalized to show the effect per decade that was mediated by these practice measures... Positive mediation is where changes in certain mediators result in more improvement in survival (partly explaining the time trend), and negative mediation is where changes in other mediators result in less improvement in survival. The net effect is the net mediated change in mortality per phase over the period between phase 1 (1999-2001) and phase 5 (2012-2015); i.e. the sum of the positive and negative mediating effects within that model on a log scale.

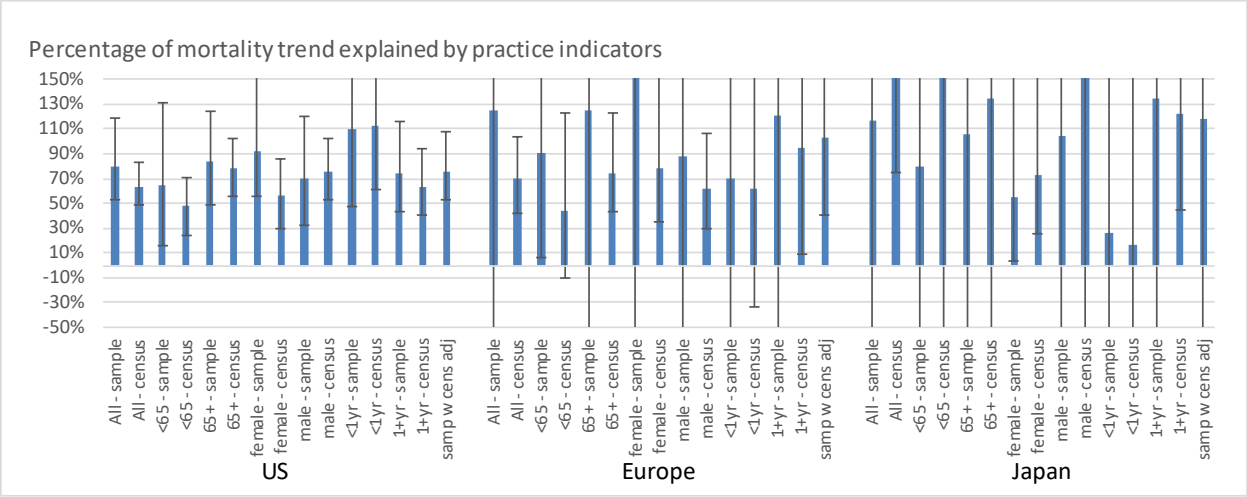
All potential mediators in each region were considered together in the same AFT model, and each separate linear model on each mediator included the other mediators as predictors. Analyses adjusted for age, race, sex, vintage, and EHR identifier in the census-based models, or all of those variables plus 13 comorbid conditions and BMI in the sample-based models.

Supplemental Figure 2.5: Vintage distribution for patients with residual urine volume, without residual urine volume, and with missing data on residual urine volume



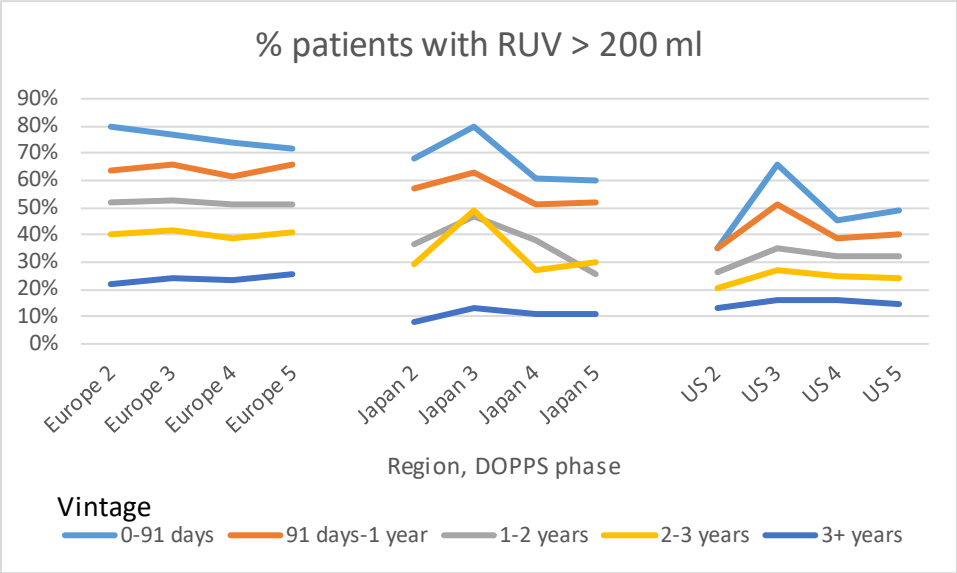
Legend:
For the residrenal_yes variable, 1 indicated that the patient had >200 ml/day urine production, 0 indicated that the patient had less than 200 ml/day, and "." Indicated missing data.

Supplemental Figure 2.6: Percentage of mortality trend explained by practice indicators, by region (US, Europe, Japan), for sample patients and for census patients within each region, by category: age (<65 v. 65+), sex (male v. female), vintage (<1 year v. 1+ year), and for sample patients using census adjustment factors



Legend: Bootstrapped results (200 iterations) for confidence ranges (2.5th percentile – 97.5th percentile).
"Sample" = DOPPS sample patients, adjusted for demographics and comorbid conditions.
"Census" = Full DOPPS census, adjusted only for vintage, age, black/non-black, EHR status (US), and sex.
"All" = No additional filters on age or vintage
"<65" = only patients aged <65 at the beginning of follow-up
"65+" = only patients aged 65+ at the beginning of follow-up
"<1yr" = only patients with less than one year of dialysis (vintage <1) at the beginning of follow-up
"1+yr" = only patients with more than one year of dialysis (vintage 1+) at the beginning of follow-up
"samp w cens adj" = using sample patients only, but restricting the adjustments to those used in the census
See Table 2.1 for counts of patients used in each model (sample and census, within each region).
The range of the percentage of the mortality trend explained, using the overall effect as a denominator, was quite large, due to the fact that the confidence interval for the overall effect (the denominator) tended to be close to, or in some cases overlap, zero, as shown in Table 2.3. This has been documented as an issue with this statistic when the confidence interval for the overall effect comes close to zero. [36]

Supplemental Figure 2.7: Trends in Residual Urine Volume (RUV) at study entry over DOPPS phase, stratified by vintage.



Legend: Prevalence among patients with non-missing data on a yes/no variable indicating urine output of >200 ml/day as of study entry among the prevalent cross-section of patients at the start of each DOPPS phase.

Supplemental material: staffing ratios.

Other practices can be reasonably hypothesized to impact patient survival, such as patient-staff ratios (e.g. average number of patients per full-time nurse or non-nurse staff), which have been found to be positively associated with higher hepatitis B (HBV)[37] and hepatitis C (HCV)[38] incidence. We used unit practice survey data on staffing ratios, taken from the first year questionnaire for phases 1-4, and from the year 2 questionnaire in phase 5. These staffing ratios were investigated as potential mediators. While most of the results were very similar (supplemental figures 2, 4), the inclusion of this covariate unexpectedly strengthened a negative association between IDWG < 5.7% and survival in Europe. The AFT model covariate went from 0.015, with a 95% confidence interval of (-0.494 to 0.573), in the census model without staffing ratios to -0.734 (-1.443, 0.001) when staffing ratios were included. This had the effect of giving the IDWG trends in Europe a negative mediation effect on survival when staffing ratios were included. Staffing ratios themselves had very little effect on the mediation of the time v. survival association outside this anomalous result (see supplemental figures 4b, c), due to a mortality model effect whose absolute value was less than 0.03 in all regions, so these variables were excluded from the primary analyses presented in this paper.

Supplemental material: correlations between practice measures

One potential criticism of this analysis using observational data is that the practice measures we have chosen may represent general indicators of 'good' facilities, i.e. facilities with good general practices, instead of being directly linked with outcomes. While this concern is mitigated by the fact that we have chosen measures selected for guideline recommendations by multiple international organizations based on the weight of available data, we conducted additional analyses to assess the likelihood of this explanation. Treating each facility within each phase as a separate observation (as was done in the primary analyses), we assessed the phase- and region-adjusted correlations between the practice measures chosen to determine if facilities that adhere to one guideline have a strong tendency to adhere to other recommended practices. The correlations were within the -0.10 to 0.10 range except for phosphorous control (percentage of patients with phosphorous < 6 mg/dl) and Kt/V (percentage of patients with Kt/V > 1.2), which had an R value of 0.30. Removing the adjustment for phase created artificially strong associations due to the fact that facilities participating in multiple phases were undoubtedly correlated with themselves; the highest R value was 0.43 between Kt/V and phosphorous control. While these correlations could be explored further, it appears that the correlations between practice measures do not indicate a strong 'good facility' effect. Similar results have been found in prior investigations; measures of facility adherence to different recommended practice patterns tend to be independent of each other.[39]

Supplemental material: patient selection with regard to residual kidney function

A hypothesized source of improved survival has been earlier dialysis initiation over time. To address this, we adjusted analyses for residual kidney function, using a yes/no variable indicating urine output of >200 ml/day as of study entry. Supplemental Figure 2.7 shows trends of this variable within each region, stratified by patient time on dialysis at study entry. As the figure shows, these trends have not been substantial in any region for any vintage.

Chapter 3 Simulating incidence and prevalence of end-stage kidney disease (ESKD) in the United States

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Abstract

Background and rationale

End-stage kidney disease (ESKD) patients are currently identified by the United States Renal Data System (USRDS) as those formally registered as receiving maintenance dialysis or transplantation as renal replacement therapies for chronic kidney failure. At the end of 2014, there were 662,048 ESKD patients in the United States (US).[40] Among US citizens, nearly all ESKD patients are enrolled in Medicare after 90 days of treatment. The direct medical costs of ESKD to Medicare in the US exceeds $30 billion/year.[41]

While the age-sex-race-adjusted incidence rate of ESKD per million/year has declined since 2006, the crude incidence has risen[42]. Future trends in the crude incidence of ESKD are important because of their impact on morbidity, mortality, quality of life, healthcare utilization, policy and cost. We sought to model incidence and prevalence of ESKD in the US, based on population factors.

Aim

The aim of this analysis was to simulate the incidence and prevalence of ESKD in the US, based on population factors including race, age, population size, obesity, hypertension, and diabetes, and ESKD factors including death rates.

Data and methods

We used an open compartmental simulation model to simulate transitions between obesity, diabetes, hypertension, and ESKD for age- and race-specific demographic groups, using restricted cubic spline estimates of time-varying flow parameters based on annual incidence between 1980-2013. Parameter estimates were obtained via Nelder-Mead optimization of the sum-of-squared errors in yearly incidence. Data sources included the Centers for Disease Control and Prevention National Health and Nutrition Examination Survey (CDC NHANES), the Centers for Disease Control and Prevention National Health Interview Survey (CDC NHIS), the United States Renal Data System (USRDS), and the US Census.

Results

Age- and race-specific ESKD incidence and prevalences can be modeled for most age/race groups from 1980 through 2013, with prevalences within 19% of the actual rates for 95% of the observations (individual years for each age and race group). The simulated rates that result from current population aging and obesity trends seem to follow past age-specific and overall incidence trends.

Conclusion

The elements selected for this simulation model are sufficient for reasonably accurate estimates of the overall ESKD incidence and prevalences, based on demographic changes and changes in obesity and diabetes prevalence in the general population. These methods and the resulting model can serve in the future as a basis for projecting these trends in order to predict resource allocation needs for the ESKD population.

Introduction

The Medicare Entitlement Act of 1972 allowed people of all ages with kidney failure to receive Medicare coverage.[43] Among patients with end-stage kidney disease (ESKD), defined as requiring chronic treatment for terminal kidney failure, 79% had Medicare in 2013 as either the primary (416,808 patients) or secondary (57,677 patients) payer.[44] These patients represent 1% of the Medicare population, but account for 7% of Medicare's expenditures.[45]

The incidence rates of ESKD have generally increased since 1980. Figure 3.1 shows trends in the crude (unadjusted) incidence rate of ESKD stratified by the primary cause identified on the Medical Evidence Form (CMS Form 2728). Form instructions indicate that cause of ESKD is to be designated by the treating physician who certifies onset of renal replacement therapy (typically dialysis or transplantation) for ESKD.

The age-sex-race-adjusted incidence rate of ESKD has leveled off and has declined since 2009.[46] This may have resulted, in part, from the decrease in age-specific incidence of ESKD attributable to diabetes.[47] On the other hand, census projections based on declining death rates in the general population and changes in the racial demographics of the country estimate an aging, more racially mixed general population which forms the at-risk pool of potential ESKD patients. The ability to simulate the associations between demographics, risk factors, and the ESKD population is of considerable interest since changes in ESKD trends have the potential for large impacts on public health, resource allocation, and costs.

Simulations of ESKD incidence and prevalence have been performed several times using different methods. Port[48] used two different methods on data through 1997 - exponential increase versus constant increase - to successfully predict ESKD growth through 2000; the actual rate was between these two estimates. Xue et al.[49] predicted within 10% of the actual number of incident and prevalent cases in 2010, using a stepwise autoregressive method with exponential smoothing.

The Gilbertson et al.[50] simulation model related the size of the diabetic and non-diabetic populations, both generated using linear projections, to project ESKD incidence and prevalence. They used CDC National Health Interview Survey (NHIS) data in a compartmental model with compartments defined by incidence, prevalence, diabetes status, and mortality over seven age groups, three race groups, and two diagnosis groups (diabetic and non-diabetic).This simulation model over-estimated the incidence rates and counts of the ESKD population after 2005.

These prior simulations did not adequately capture the potential impact of important determinants of ESKD risk, such as obesity's impact through diabetes. In order to do so, we have developed a compartmental model that incorporates contemporary trends in population demographics, obesity, diabetes, and hypertension, in order to more accurately model ESKD incidence and prevalence during the period from 1980-2013. This simulation model could be used in future analyses designed to project trends in ESKD incidence and prevalence based on expected population demographic changes in the near future.

Methods

Demographic categories

There are many population factors that influence the incidence and prevalence of ESKD. Some factors identified as important in previous literature include age (adjusted hazard ratio [HR] of ESKD incidence = 1.60 {1.21-2.10} for age 55+ v. age <55 years), race (adjusted HR = 2.47 {1.17-5.21} for black v. white), sex (adj. HR = 1.49 {1.10-2.01} for male v. female), comorbid conditions such as hypertension (adj. HR = 1.44 {1.31-1.59} per 19 mmHg higher systolic blood pressure) and diabetes (adj. HR = 6.10 {4.57-8.13} versus people without

diabetes), BMI (adj. HR = 1.13 {1.00-1.29} per 1 kg/m^2 increase), and ethnicity (historically, adjusted incidence rates among Hispanics have been 1.35-1.95 times higher than among non-Hispanics). [51,52] Many of these factors have been the focus of USRDS Annual Data Reports, which show large differences in ESKD incidence rates for different demographic and clinical groups.[53] The age and race distribution of the United States are changing over time, and the influences of these demographic shifts on ESKD trends should be accounted for in the simulation.

While ideally we would consider all individual risk factors for ESKD, including race, ethnicity, sex, more specific diagnosis categories (e.g. tracking specific glomerular diseases separately), genetic predictors, and various comorbid conditions, the estimates within individual categories of specific demographic, diagnostic, comorbid, and genetic factors for this analysis would be extremely unstable (if data were available at all), and definitions for some of the categories have changed over time. For example, the US Census has stated that racial data from the 2000 US Census are not directly comparable to data from earlier censuses.[54] Similarly, the USRDS and the census ethnicity data collection have changed over the years in ways that impacted reporting.[55,56] We have analyzed models using different racial categorizations to test the sensitivity of our results to different racial categorizations. Some simulations were based on white, black, and other race to clearly identify the groups that are the largest outliers in both incidence and death rates. Other simulations were based on white versus non-white race to maximize stability; the full range of results is reported across all simulations.

Within each racial group, we further categorized patients within four age groups (<45, 45-64, 65-74, and 75+), and three diagnosis groups (diabetes, hypertension, and all other causes of ESKD). Since treatment and associations with obesity may differ for people with hypertension, people with diabetes, and patients with other diagnoses, the incidence trends among people with hypertension may differ from those of other causes, and were thus tracked separately. All rates used were based on adults (18+), as these represented the experience of the vast majority of the at-risk population, even in this youngest age group. Even among those in under-45 age group, only 6% of ESKD cases were under age 18.

Census data for our analyses used US Census Statistical Abstracts of the United States.[57] A weighted average was applied throughout each age/race group's estimates to smooth changes in count or trajectory due to changes in the definition or reporting of racial groups.

Obesity prevalence

The 'obesity epidemic' dramatically changed the risk profile of the general population with respect to several factors potentially related to ESKD. For the simulation models, obesity (defined as BMI 30+ kg/m^2) estimates were obtained from NHANES for each race and age group.[58] Different estimates were obtained using both within–age- race category smoothing and by assuming that within-race distributions across ages were similar; the latter data were used for sensitivity analyses. To simulate an obesity downturn, we used a quadratic regression fit to data from 1989 to 2012, which assumes that obesity prevalence has plateaued and will eventually fall.

A linear regression fit over the same period was used to illustrate the assumption that there will be a continued rise in obesity prevalence.

Simulation modeling approach

There are many different types of simulation models. While agent-based models can more easily handle detailed influences of subject-level characteristics on between-subject interactions when modeling infectious disease transmission risks, our analysis is focused on a chronic disease; between-subject transmission is not likely to modify population trends. The compartmental model has been used successfully in the past for chronic disease, and is computationally simpler, since it does not require tracking individuals and their interactions.[59]

In this simulation, the compartments and flows (transition rates) used in each of the simulation models are diagrammed in Figure 3.2. After diabetes prevalence was estimated using obesity and demographic data, in the diabetes simulation model, the results were used in the ESKD simulation model as inputs, along with general population size, hypertension prevalence, 'other' diagnosis ESKD incidence rates, and the remaining ESKD data. The outputs of the ESKD simulation model include ESKD incidence, prevalence, and deaths for each year for each demographic and diagnosis group of patients.

Transition rates to ESKD are modeled as constant within each year, but changing from year to year. Nelder-Mead optimization[60] (via the "optim" function in R[61]) is used on the sum of squared error in the incidence rates to obtain the estimated rates and their trends. Trends in these rates over calendar years are modeled as restricted cubic splines, to allow their estimation to be

both data-driven and to smooth any sudden changes. Knots at 1988 and 1999 were chosen based on the fit of the overall simulation model, not individually for each race-age-specific simulation model. Simulations for the obesity-to-diabetes transition in the population were constructed separately for ESKD incidence "caused by" diabetes and for ESKD incidence "caused by" hypertension. Each of these simulations was modeled separately by age-race group, with separate rates calculated within each group. The rates were generally small, so we did not separately model the reduction in the 'at risk' population due to (for example) the proportion of patients developing ESKD. This means that we are assuming, for example, that the general population of people with hypertension but without ESKD will not be substantially diminished in any given year by the number of incident cases of ESKD caused by hypertension.

Programming for the simulation model was performed using the R v. 2.15.0 statistical package.[62]

Equations

Each "compartment" in a compartmental model is a relevant population group, e.g., people with diabetes or people who have died. Populations can enter and leave these compartments. "Sources" in a compartmental model are special compartments from which the relevant population originates. The size of a source influences the incidence, or 'flow' into the next compartment. For example, if the population of people with obesity is larger, then it is expected that more people develop diabetes in a given year. Usually there are no flows into a source. "Sinks" are special compartments that the population cannot leave(i.e., "death"). Compartments, sources, and sinks used in the simulation model were defined as follows.

General population (Gp) for a given year and demographic (age-race) group (DG) (source) = Gp(year, DG)

- Based on US Census data, with smoothing to handle changes in racial prevalences produced by changes in the methods (e.g. sampling) and the question format.

Population obesity (source) = P_{Ob} (year, DG) = Gp(year, DG) * Obesity prevalence (DG)

- Obesity prevalence (DG) from NHANES obesity data with linear interpolations
- See "Obesity prevalence"

Population diabetes (compartment) = P_{dm}(year, DG) = P_{dm}(year-1) + P_{ob}(year-1)*(1-exp(-λ_{DM}(DG))) – P_{dm}(year-1)*(1-exp(-$\lambda_{DM\text{-}dth}$(DG)-$\lambda_{DM\text{-}dth\text{-}change}$(DG)*((year>1991)*.1*(year-1991)*(year<2002)+(year>2001))))

- λ_{DM} (DG)= Rate, transition from obesity to diabetes per year for each DG
- $\lambda_{DM\text{-}dth}$(DG)= Rate, transition from diabetes to death per year for each DG
- $\lambda_{DM\text{-}dth\text{-}change}$(DG): Allows for change in $\lambda_{DM\text{-}dth}$(DG), to account for indications that the death rate for people with diabetes may have improved.[63]
- See "Diabetes prevalence"

Population Hypertension compartment) = $P_{Hypertension}$ (year, DG) = Gp(year) * hypertension(DG) prevalence data

- Hypertension(DG) prevalence data used from published sources for each DG
- See "Hypertension prevalence"

ESKD(year, DG) (compartment) = ESKD(year-1, DG) + (Source({cause} , year-1, DG)*(1-exp(-$\lambda_{RCS\text{-}ESKD\{diabetes,\ hypertension\}}$(DG) - $\gamma_{ESKD\{other\}}$(DG))) – ESKD(year-1)*(1-exp(-γ_{Dth}(DG))))*(exp(-0.5*γ_{Dth}(DG))) - ESKD(year-1, DG)*(1-exp(-γ_{Dth}(DG))) - $\gamma_{emigration}$(DG)*ESKD(year-1,DG)

- {Cause} categorized as diabetes, hypertension, other
- Source{cause} = source population of cause: population with diabetes, population hypertension, or whole population. Incidence for each diagnosis is added to the ESKD compartment. The death rate among incident patients, assumed to have an average of half of a year of follow-up, is applied across the sum of all incident patients (thus the exp(-0.5*γ_{Dth}(DG)) term).
- $\lambda_{RCS\text{-}ESKD\{diabetes,\ hypertension\}}$ (DG): Represents terms used in restricted cubic spline (RCS) for the rate of transition from source{cause} to ESKD per year
- $\gamma_{ESKD\{other\}}$(DG) = Other cause (non-hypertension, non-diabetes) transition rate
- γ_{Dth}(DG) = Transition from ESKD to death. Note that death rates are not calculated for each individual cause.
- $\gamma_{emigration}$(DG) = Transition from ESKD to loss of follow-up or emigration (e.g. emigration from the United States) as a percentage of previous prevalent population

Death (sink): not tracked separately, used for illustrative purposes

Attrition(sink): not tracked separately, used for illustrative purposes. This includes actual emigration from the United States as well as loss to follow-up for other reasons.

Legend: "Year" indicates the calendar year, and "DG" indicates the demographic group (age-race category). Each rate labeled with the Greek letter lambda λ is estimated using the Nelder-Mead optimization to minimize the sum of the squared differences between actual and simulated ESKD incidence. Other transition rates indicated with the Greek letter gamma γ are taken from actual rates. Flows are modeled as being strongly influenced by the size of each source population;

however, this model does not assume that patients explicitly move from one compartment to another. Patients are not tracked individually, and the overall size of a population generally increases as calendar time increases.

Diabetes prevalence

Our approach for modeling diabetes focused on predicting diabetes using the obese population. Obesity is a recognized risk factor for diabetes.[64] About 95% of adults diagnosed with diabetes in the U.S. have type 2 diabetes,[65] and similar ratios are shown in retrospective cohort studies of CKD incidence among people with diabetes.[66] Eighty (80) percent of this population is overweight or obese,[67] and 35%-57% of adults with diabetes were obese.[68] Two potential sources of long-term surveillance of the diabetes population are the NHANES data and the CDC. The NHANES data allow independent verification of the diabetes diagnosis using laboratory data. The prevalence of diabetes varies by source and definition, being lowest for the NHIS survey (self-reported), higher for NHANES (diagnosed), and highest using diagnoses and lab-based criteria (e.g., hemoglobin A1c 6.5%+).[69] It seems probable that people with diabetes who develop ESKD have become aware of their diabetes by the time they are diagnosed with ESKD, since this process takes 10-25 years and ESKD onset is usually preceded by clinical/laboratory signs such as retinopathy or proteinuria.[70] This makes the self-aware diabetic population a more precise denominator than the entire diabetic population for describing the population at risk of ESKD. For these reasons, and because the larger CDC NHIS sample size and more frequent data collection allows for more stable estimates of diabetes in specific age-race groups, we have used the CDC estimates of diabetes prevalence.

Data for the black population were used to approximate simulation model inputs for "non-white" sensitivity analysis runs in the diabetes simulation model. Native Americans have higher rates of diabetes than blacks, and Asian Americans have lower rates of diabetes than blacks, although there are fewer native Americans than Asian Americans.[71] Stable estimates on each of these individual populations within each age group were not obtainable for all the years used in the simulation models.

The transitions from obesity to diabetes and from diabetes to death were modeled as latent transition rate variables. The diabetes death rate was allowed to smoothly change over a period between 1991 and 2002 to reflect possible improvements in diabetes care; improvements on the death rates among diabetes around this period have been reported in the literature.[72] While the initial estimates for the optimization procedure were taken from the literature, the death rates among people with diabetes were not obtained from data; instead, this variable, along with incidence and the change in death rates, was modeled as a latent variable, optimized to match the prevalent diabetes population trends.

Hypertension prevalence

Hypertension in the NHANES data was defined as having any of the following indicators: a systolic blood pressure (SBP) of 140 mmHg or greater, a diastolic blood pressure (DBP) of 90 mmHg or greater, taking antihypertensive medicine, or having been diagnosed as having hypertension at least twice.

Hypertension was more prevalent among the older population, with 78% of the general population over 75 years of age having hypertension, versus <25% among those under age 45 in 2007-12. Over 40% of the black population had hypertension during this period, versus 27-30% for other races.[73]

Although Narkiewicz[74] has claimed that two-thirds of hypertension is related to obesity, the prevalence of hypertension has not been rising nearly as much as the prevalence of obesity (supplemental figure 3.1). Whites and blacks generally had a 2-5% increase between 1988-94 and 2007-2012,[75] but this may have been due to aging. The median age among whites increased from 32 years in 1980 to 39 years in 2000, and among blacks median age increased from 25 to 30 over the same period.[76]

Note that while the overall proportion of people in the NHANES data with hypertension has not changed much, the proportion of the population with hypertension who has SBP or DBP above the threshold seems to have been decreasing in all age groups (supplemental figure 3.2). Overall, 83% of the people with hypertension had SBP or DBP above the threshold in the 1976-1980 data, but in the 2009-2014 data this proportion ranged from 40-42%. The proportion of people with hypertension in the 1976-1980 data who were prescribed anti-hypertensive medication was 24%, while in the 2009-2014 data it ranged from 76-77%.

As a sensitivity analyses, simulations were performed using published data to estimate hypertension prevalence between 1980 and 2012. [77] We assumed that the distribution of hypertension by age was similar within race groups. Since the data within age groups had larger

sample sizes than the data within age/race groups, this avoided some of the instability that was present in some of the within-age/race group estimates of hypertension prevalence, effectively smoothing the trends in hypertension prevalence.

ESKD incidence and subtypes

ESKD incidence attributed to diabetes or hypertension as the primary cause

ESKD incidence data were obtained from the USRDS RenDER system.[78] The incidence rates of ESKD subtypes for which the primary cause was attributed to diabetes and to hypertension were estimated each year since 2012 separately for each age-race group. See the simulation modeling approach section for a description of transition rate parameter estimation.

ESKD incidence attributed to other causes

The USRDS attributed 73% percent of all ESKD incidence diagnosed in 2013 to diabetes or hypertension as the primary cause.[79] The remaining ESKD subtypes were 'other' (9%), glomerulonephritis (8%), unknown/missing (7%), cystic kidney disease (2%), and other urologic disease (1%). While most of these ESKD subtypes seem to have reasonably linear trends over time, there was a marked decrease in the slope of ESKD incidence attributed primarily to glomerulonephritis during the 1990s, possibly linked to increasing use of immunosuppression to combat the progression of chronic kidney disease among those patients, or possibly due to lower detection rates. Data before 1985 seem to be unstable and may reflect data-collection issues early in the USRDS data-collection process.

ESKD death rates

ESKD death rates were obtained from the USRDS RenDER system.[80] The death rate among ESKD patients has decreased over the past two decades, both overall and within specific age groups.[81] The simulation does not include a direct relation between obesity and ESKD death, e.g. attempting to model the effects on death rates of a more or less obese ESKD population. This direct relation is known to be counterintuitive, with obesity typically associated with better survival among ESKD patients.[82] Since this relation is not completely understood, we simply used overall ESKD death rate trends instead of attempting to separately simulate the association between ESKD death rates and obesity.

Population movement and loss to follow-up

The prevalent ESKD population has been growing each year. While a small number of patients recover enough kidney function to stop dialysis (possibly due to having been incorrectly classified as ESKD), the most frequent way to leave the ESKD population is death. While death-rate trends are modeled and included, the prevalent populations would be increasingly inaccurate if other departures, such as loss to follow-up, were not accounted for. Patients are considered lost to follow-up if they have no treatment claims for a year. Loss to follow-up may include a death that wasn't recorded, emigration from the United States, or other causes. It is possible that some of these patients were transplant recipients under the age of 65 whose Medicare benefits ended three years after their transplant. Note that voluntary withdrawal from dialysis is not usually a reason for a patient being lost to follow-up; their death should be reported to Medicare despite the fact that they chose to discontinue dialysis.

Since 2000, our analyses of USRDS data indicate that 1000-5000 ESKD patients (0.5-0.9% of the prevalent population) seem to be departing the US ESKD population each year,

without recorded death. These departures are calculated as the difference between the actual prevalent growth and the expected prevalent growth, based on ESKD incidence and deaths during the year. Similarly, the within-age/race-group net gains and losses, including overall losses to follow-up, from each age/race group were accounted for using proportional net changes.

Results

Diabetes modeling

Figure 3.3 shows the annual point prevalence of diabetes on December 31 of each year from 1980 to 2013, by race (5A) and age (5B), as a percentage of the population, as well as the curves simulated using population obesity data. The use of obesity data to predict trends in the empirical data seemed to result in trends that match observed data and parameter estimates that match published literature reasonably well.

Comparison of simulated diabetes progression rates to literature

The simulation model produced estimates for a rate parameter defining the diabetes incidence based on the obese population for each age and race group. These estimates varied widely, from 0.03 for whites under age 45 to 0.39 for blacks over age 75 years. Older patients had higher incidence rates, as did black patients. These results matched CDC findings comparing relative diabetes incidence among different age groups and races.[83,84] While incidence rates for specific demographic categories are difficult to find in the literature, the overall rate of 0.016 is similar to the rates reported elsewhere. For example, Fox et al. found that 65/593 obese participants aged 40-55 in samples taken during the 1980s and 1990s progressed to diabetes over 8 years, which corresponds to an average incidence rate of 0.015/year..[85]This result indicates that our rate is not outside reasonable bounds of diabetes incidence rates among obese populations.

The death rates and departure rates among diabetic patients were allowed to change over time, since Gregg et al. have published data showing that these rates are decreasing.[86] While the rates were fairly variable between age/race groups, they generally decreased over time. The death rates among diabetics in the simulation were much higher (ranging from 0.10/year. in 1980 to 0.044/year. in 2010 in the overall population, or 0.066/year. in 1997 and 0.044/year. in 2004) than in Gregg et al. (varying between 0.015 and 0.021 between 1997 and 2004). This difference may result from the fact that the Gregg et al. results were standardized to a population about 15 years younger than the average diabetic population. This difference would be compatible with a three-fold increase in death rates among patients with diabetes between age 45 and 60, which corresponds to what has been found in other publications.[87]

ESKD Incidence modeling

ESKD incidence was modeled separately for diabetes, hypertension, and other ESKD "causal" subtypes for each age and race category. The results were combined for overall estimates and for race- and age-specific reporting.

Figure 3.4a shows the annual ESKD incidence rate from 1980 to 2013 by race. ESKD incidence continues to be lower for whites than for blacks, and the patterns of simulated incidence are close to observed trends. The simulated incidence for whites rose smoothly, with the simulated results matching the actual results well. For the other race category, incidence rates started dropping sharply around 2000, which is the year when the size of this age category increased in the U.S. Census (the denominator). Incidence counts per year (the numerator) in the

other race category increased during 2000-2013 by 1,300 (24%) in the simulation model's estimates and by 900 (14%) in the reported data.

Figure 3.4b shows the annual ESKD incidence rate from 1980 to 2013 by age group. The ESKD incidence rate was greater for older adults, especially after the late 1980s. The simulated temporal trend was rather flat after the year 2000 for those under age 45, remaining within a range of 74-80 per million per year in the reported data or the simulation model's estimates. For people aged 45-64 the trend was rising slightly, from 514 to 543 per million per year (simulation model's estimate) and 525 to 537 per million per year (reported data) between 2000 and 2013. There was a decline in the incidence for those aged 65-74, from 1237 to 1149 per million per year (simulation model's estimate) and 1281 to 1151 per million/year in 2013. The rate among those aged 75 and over was more variable, and the simulation model did not capture the observed drop between 2010-2013 from 1518 to 1391 per million/year.

Comparison of simulated ESKD incidence rates to literature

Generally, the incidence rates calculated for each age and race group increased prior to the mid-1990s. For diabetes incidence, the rates decreased slightly afterwards; for hypertension, the incidence rates were generally constant after the mid-1990s. The overall ESKD incidence rates among the age and race groups with diabetes or hypertension range from a number indistinguishable from <0.001 per hundred per year for white patients with diabetes over age 75 in 1980 up to 0.5-0.8 per hundred per year for black patients with diabetes in the mid-1990s. These results are generally consistent with data from other sources that show higher incidence for blacks and greater increases in ESKD incidence since 1980 in the older population.[88,89] While

the incidence rates in the general population have tended to be lower (<0.2 per hundred people per year), these results are reasonably consistent with the literature after accounting for the relatively higher incidence rates for people with diabetes and hypertension. Narres et al. found incidence risk ratios of 6.2-12 across different studies of white populations with diabetes versus those without diabetes, and risk ratios of 2-4 for blacks with diabetes versus blacks without diabetes.[90] Ravera et al. found risk ratios exceeding 20 for people with stage four hypertension (SBP > 210 or DBP > 120 mmHg), versus optimal levels, and progressively lower risk ratios for various levels of hypertension between these levels.[91]

While specific incidence rates for specific demographic groups are difficult to obtain from the published literature, the incidence rates by age and by race obtained through simulation modeling seem to be ranked among the demographic groups in a manner consistent with the relative rates reported in the published literature.

ESKD prevalence modeling

ESKD death-rate estimates were combined with ESKD incidence estimates (as shown in Figure 3.4) to estimate trends in ESKD prevalence. The increasing incidence rate along with the increasing size of the United States population and the generally decreasing age-specific ESKD death rates mean that the number of prevalent ESKD cases generally increased throughout the simulation period from 1980 to 2013.

Figure 3.5 shows annual ESKD prevalence (per million) by race (8a) and by age (8b). While the fit is generally good, the data leading up to 2000 was more problematic for other race

and for 75+ prevalences. These arise from over-estimation of ESKD incidence rates for these groups (see Figure 3.4). The simulation model's estimates were generally closer to the reported data later on, after 2000 for the other race group and after 2005 for the population over the age of 75.

Discussion

The simulation model appears to be able to capture observed trends in ESKD incidence and prevalence using population inputs, including the size of the population, the demographic composition of the population, population obesity, diabetes, and hypertension prevalence, and USRDS estimates of ESKD incidence and death rates. The non-linear trends in incidence and prevalence were reasonably close to the reported data for the demographic groups studied, and the parameter estimates used were generally smooth and followed patterns that would be predicted based on published literature. The exception--diabetes death rates--could be explained by the fact that the published rates were age-standardized to a younger population. Note that unilaterally changing the diabetes death rates in the simulation would result in estimates that would fit the general population data less well than the current estimates.

Hypertension prevalence seems to have been surprisingly stable, given the obesity epidemic. The composition of the population with hypertension changed radically over this period. The proportion of the population identified as having hypertension due to a prescription for anti-hypertensive medication increased dramatically while the proportion defined as having hypertension due to SBP or DBP levels decreased. Increased treatment and control of hypertension may be behind the relatively constant prevalence of hypertension.

Despite the steady or decreasing age-specific incidence rates of ESKD since 2009,[92] the annual number of incident cases and the crude incidence rate has generally risen, as has the number of prevalent cases and crude prevalence of ESKD. Part of this increase in prevalence has been due to falling death rates in the ESKD population during this period. Using CDC data on death rates, we estimated that, over the same period, age-specific death rates decreased by an average of 0.5-1.7%/year among adults in the general U.S. population.[93,94] This was a slower rate of decline in every age group than was seen for the ESKD population.

The age-sex-race-adjusted incidence rate of ESKD has declined since 2006.[95] This has been reflected in the fact that the age- and race-specific incidence used to generate the simulation has been either stable or decreasing. On the other hand, more of the population is in the older age groups now, which are associated with higher incidence rates of ESKD. So even though the within-age-group incidence is steady or declining, the overall crude ESKD incidence rate has offset this within-age-group trend, resulting in an increasing crude (unadjusted) incidence rate.[96] Similar effects have been seen in Japan, where despite declining age-specific incidence rates the crude incidence has increased due to an increase in the age of the general population that has been even more extreme than what the United States is experiencing.[97]

Generally, the parameter estimates obtained within the simulation for transition rates between various compartments were consistent with those in the published literature. The death rates among diabetic individuals in the simulation were higher than indicated by one published source, but this difference may have resulted from differences in the age distributions of the populations compared.

The greater discrepancies between the reported data and the simulation model's estimated incidence for the population over the age of 75 years could reflect factors affecting incidence in this population not captured by the simulation model, as well as random variation in the age group that had the fewest ESKD patients during this period. On the other hand, the discrepancy between the simulation model's estimated incidence for the 'other' race group and the reported data for this group might be more easily explained. There was a change in the data collection methods used by the US Census that disproportionately increased this group's population in the year 2000. Despite the fact that we attempted to smooth this change using weighted average estimates over ranges of years, this change in census methods still created an artifact in the curve that the simulation model was unable to completely reproduce.

The simulation did not capture the sudden drop after 2010 in incidence among individuals of black race (Figure 3.4a). Similarly, the simulation did not capture the sudden drop after 2010 in incidence among the population over age 65. Data over the next few years will help determine whether this drop is due to random variability, reporting lag, or changes in 2010 census estimation techniques; or whether it reflects real changes in the underlying factors driving ESKD incidence in black and older adults. The most recent USRDS ADR shows a slight increase in incidence among black individuals in 2014, 718 versus 703 per million per year in 2013.[98]

Limitations

The current simulation model of diabetes as a single compartment is overly simplistic. Not all ESKD among patients with diabetes should be attributed to diabetes. Eighty percent of the incident ESKD population with diabetes have diabetes listed as their primary cause of

disease.[99] Analyses of biopsy results among ESKD patients with diabetes similarly show that 79% of these patients have biopsy-verified diabetic glomerulosclerosis (79%).[100] Using the size of the entire population of people with diagnosed diabetes to as a predictor to estimate diabetes-caused ESKD incidence implicitly assumes that there are no major shifts in the proportion of patients with diabetes-caused ESKD among ESKD patients with diabetes. More complete national data collection on people in various stages of diabetes would allow more specific identification of the population at risk of ESKD within the population of people with diabetes.

In an effort to somewhat limit the diabetes population to those who were more likely to be at risk of ESKD incidence attributable to diabetes, we have based our diabetes analyses on CDC counts of people who were aware of their diabetes status. Diabetes normally takes years to progress among the patients who end up with ESKD. We believe that many of the people unaware of their diabetes status may be at an earlier stage of diabetes or otherwise less symptomatic and thus less at risk of ESKD. Prior research has shown that increasing diabetes prevalence has reflected a rise in diagnosed diabetes; undiagnosed diabetes has not increased in the overall population.[101] If this assumption holds, then the current analysis reflects the trends in the population most at-risk of ESKD among people with diabetes, although better identification of the distribution of well-controlled diabetes versus uncontrolled diabetes within this group might produce more precise estimates.

While this simulation model captures important features of ESKD incidence such as the contributions of obesity to ESKD through diabetes, it still omits many determinants of ESKD. Many factors may contribute to ESKD, and this simulation model summarizes many of these

into a small number of transitions. If more data become available that could provide stable, nationally representative information about those individual transition states, then it is likely that a simulation incorporating these data would produce more accurate results. The problem is that data for these are difficult to obtain. Early CKD is often undiagnosed, and kidney biopsies are generally not obtained in surveillance systems.

Conservative management is an alternative treatment for people with ESKD, i.e., managing symptoms without renal replacement therapy (dialysis or transplantation). Rose et al.[102] argued that the population facing ESKD, particularly the frail elderly, is choosing conservative management more frequently over time, although accurate counts are not yet available. The current simulation model naturally incorporates the effects of recent trends in this treatment because we are simulating incidence rates of treated ESKD. Future simulation modelers of ESKD trends may be able to obtain the data needed to describe trends in conservative management as a separate category of treatment.

Conclusions

The aging population, rising prevalence of comorbid conditions such as obesity, diabetes and hypertension, and decreasing ESKD death rates all impact ESKD incidence and prevalence in ways that can be accurately modeled using a compartmental model with smoothly shifting transition rates over time. This model could be used to investigate likely ESKD incidence and prevalence trends resulting from population demographic changes in the US over the near future.

Acknowledgment

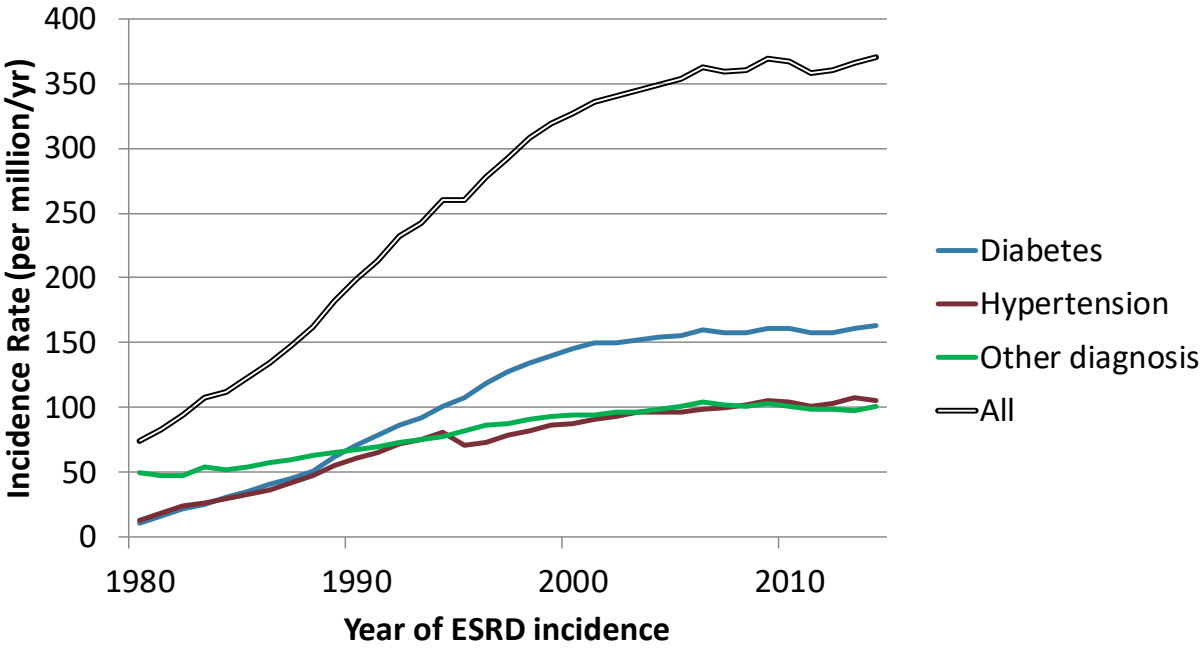
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Disclaimer

Some of the data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

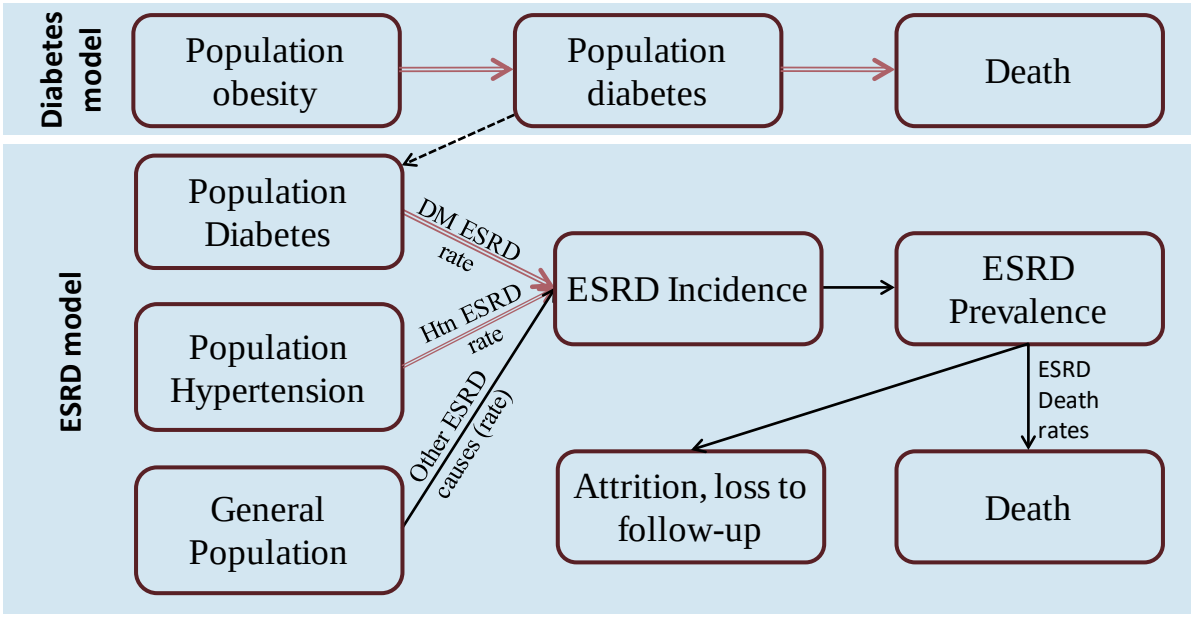
Figures

Figure 3.1: Trend in the crude ESKD incidence rate (per million/year) between 1980 and 2012, by ESKD subtype (assigned primary cause)



Legend: Data from 2014, 2016 USRDS ADR, reference table A.2

Figure 3.2: Compartmental model

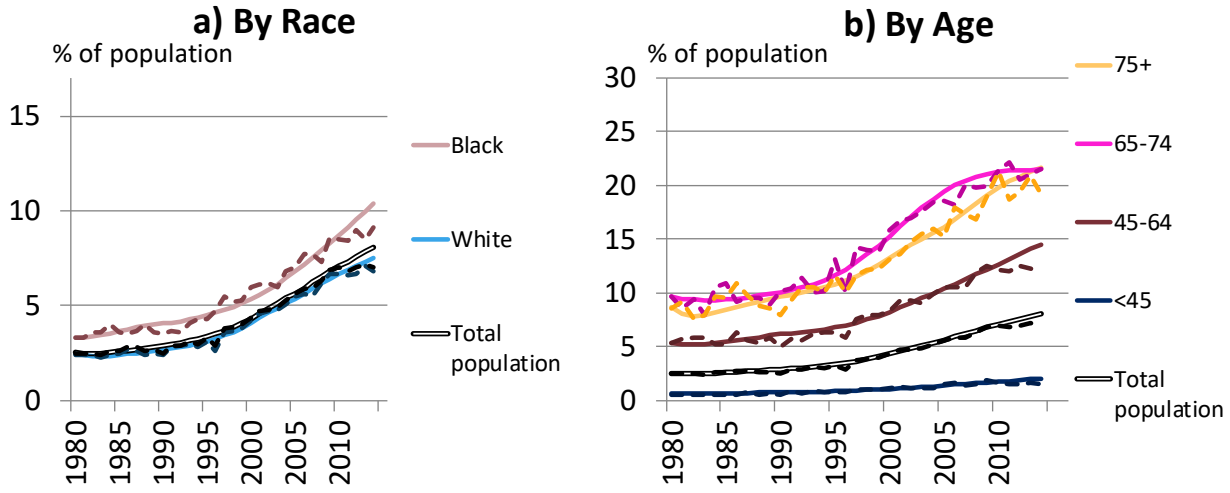


Diabetes model output used (⇢) with census data for diabetes input in ESRD model. DM/Htn/Other ESRD rate refers to ESRD where the primary cause was diabetes, hypertension, or other causes. Each arrow (transition rate) is expected to differ by age/race group and year

→ Estimated and extrapolated separately using available data

⇒ Estimated as latent variable in simulation

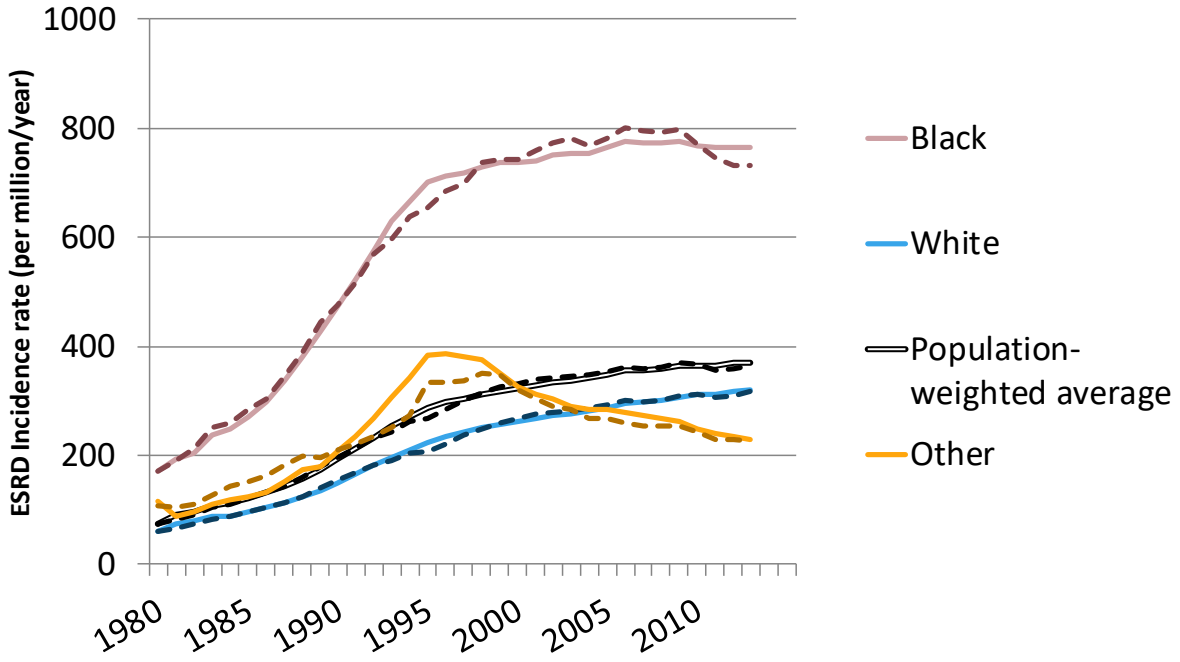
Figure 3.3: Annual diabetes prevalence from 1980 to 2013, by race (a) and age (b).



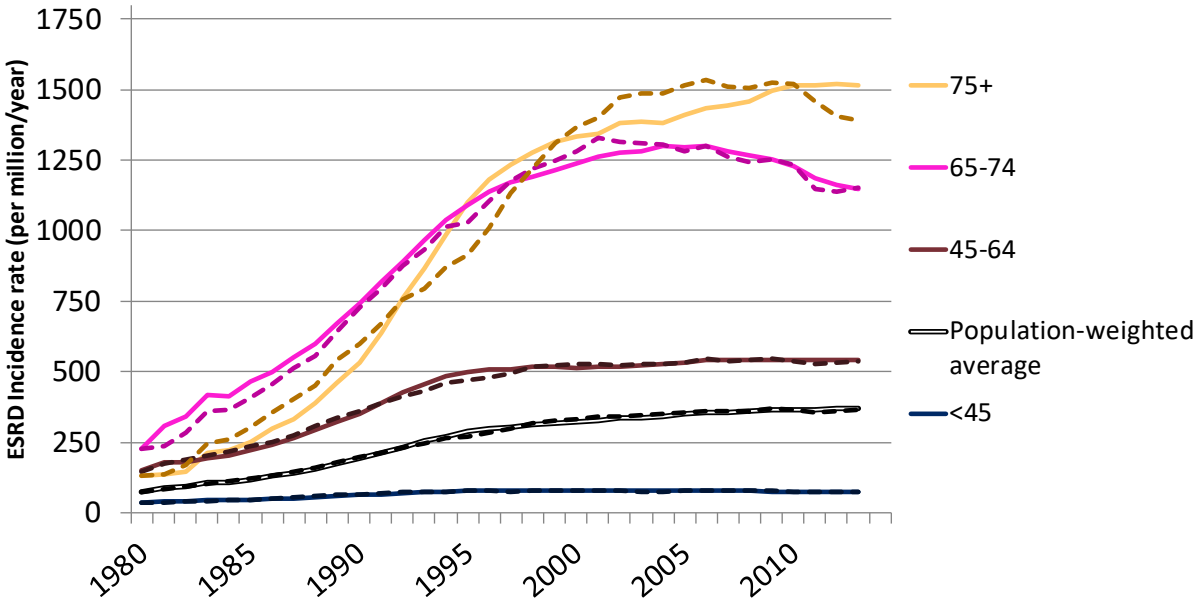
Legend: Dashed lines represent reported data, solid lines represent simulated data. Reported data on diabetes prevalence from the CDC NHIS.[103]

Figure 3.4: Annual ESKD Incidence rate (per million/year) from 1980 to 2013 by (a) race and (b) age

(a) ESKD incidence PMP by race group



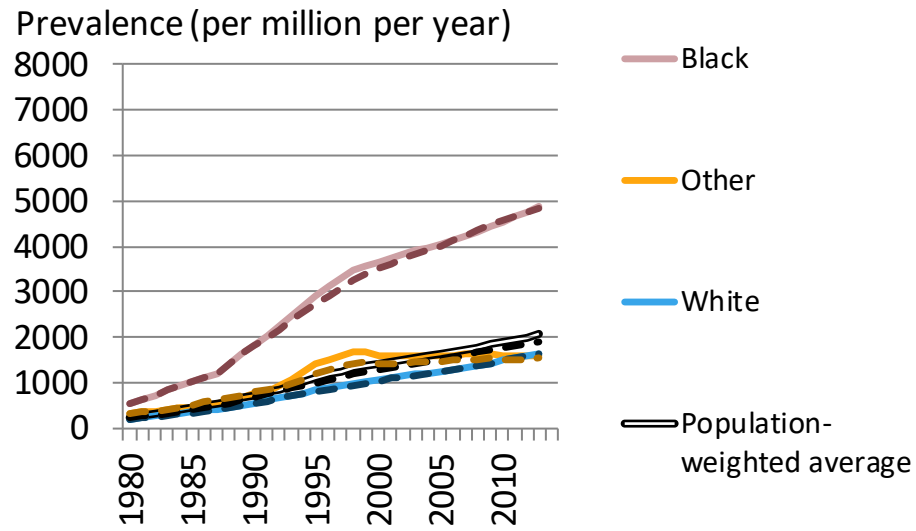
(b) ESKD incidence PMP by age group



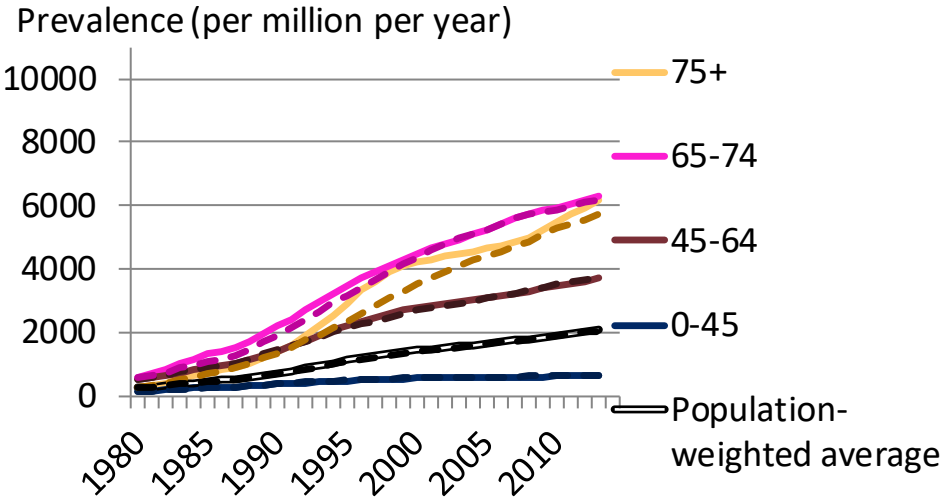
Legend: Dashed lines represent reported data, solid lines represent simulated data. Incident counts from USRDS RenDER system,[104] accessed January, 2016. Population counts from smoothed CDC-bridged US census data.

Figure 3.5: ESKD prevalence (per million per year) by (a) race group, and (b) age group

(a) Race



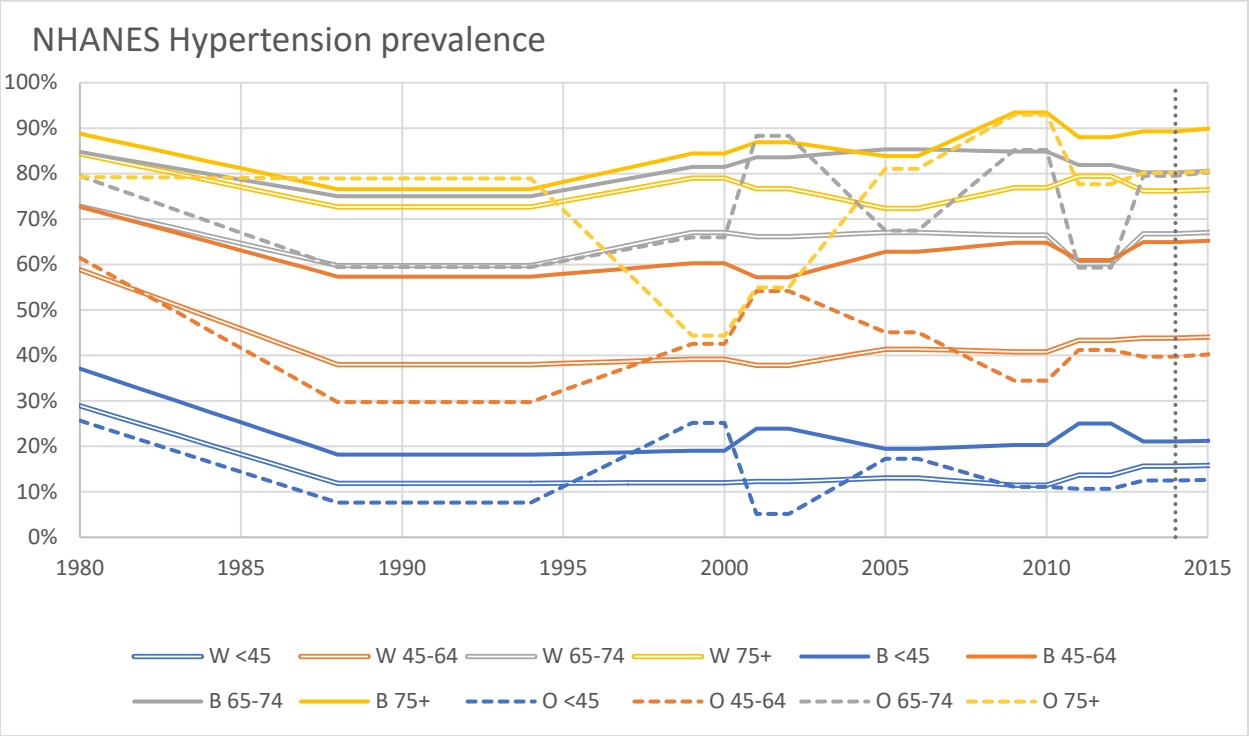
(b) Age



Legend: Dashed lines represent reported data, solid lines represent simulated data. 1980-2012 ESKD prevalent counts from USRDS RenDER.[105] Population data from smoothed, CDC bridged US Census data.

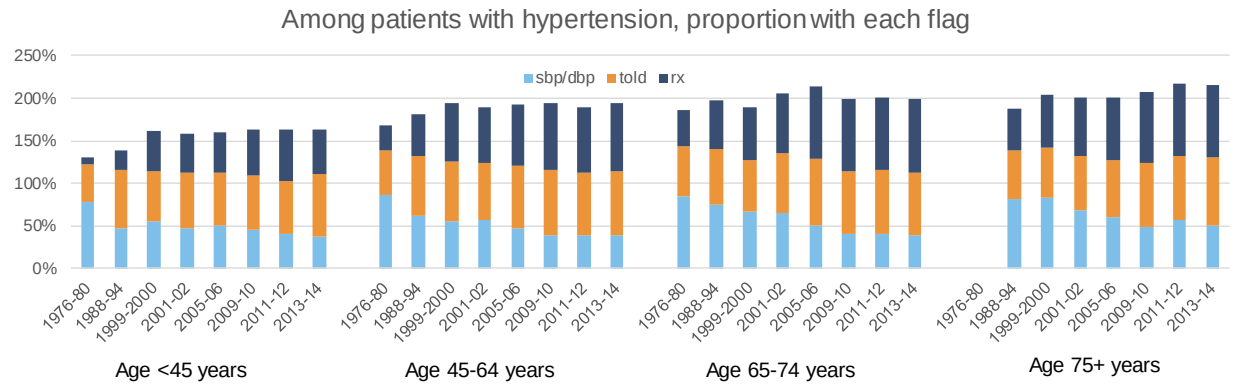
Supplemental materials

Supplemental figure 3.1: Hypertension prevalence by age group and race



Legend: NHANES data. B/W/O indicates race (Black/White/Other), while numbers indicate age groups. Hypertension was defined as having any of the following indicators: a systolic blood pressure (SBP) of 140 mmHg or greater, a diastolic blood pressure (DBP) of 90 mmHg or greater, or subject responses indicating that they were taking antihypertensive medicine, or had been diagnosed as having hypertension at least twice.

Supplemental figure 3.2: Distributions of hypertension identifiers, by NHANES cohort



Legend: These show the proportion of patients in each NHANES cohort who were identified as having hypertension by each set of criteria: "told" indicates that the patient was told twice by a physician that they have hypertension, "rx" indicates that the patient was prescribe anti-hypertensive medication, and "sbp/dbp" indicates that the patient had measured systolic or diastolic blood pressure level(s) above the thresholds of 140 and 90 mmHg, respectively. Patients may have been identified as having hypertension by more than one criterion, which is why these percentages sum to greater than 100%.

Chapter 4 Projecting end-stage kidney disease (ESKD) incidence and prevalence in the United States through 2030

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Abstract

Background and rationale

Projections of trends in chronic disease are invaluable to policy makers, healthcare providers, and researchers. The complex and highly interrelated factors involved in these trends are best analyzed using computer simulation models that are flexible enough to incorporate information from multiple, disparate sources. Herein, we have used a simulation model of the incidence and prevalence of end-stage kidney disease (ESKD) in the United States to project future trends, based on US demographic changes, obesity trends, and patient survival. These future trends in the crude incidence of ESKD are important because of the impact of this chronic condition on healthcare utilization and cost.

Aim

The aim of this analysis was to project the incidence and point prevalence of ESKD in the US through the year 2030, based on accurately modeled population trends and broad, yet plausible ranges of future changes in population obesity, which is an important part of a causal chain that impacts ESKD incidence through the increased risk of diabetes, and ESKD death rates.

Data and methods

Census data were used to project population trends through 2030. We used an open compartmental simulation model to project obesity, diabetes, hypertension, and ESKD trends, stratified by age and race, using restricted cubic spline estimates of time-varying flow parameters based on annual incidence.[106] Future trends in population-level obesity were assumed to either plateau and start to decline or to increase linearly; covering a wide range of obesity prevalence scenarios. Similarly, ESKD mortality was assumed to either remain constant at 2013 levels or to decline proportionately to 39-68% of 2013 levels.

Results

Generally, the US Census projects that the population will continue to grow, with increasing proportions of older and non-white demographic groups. While age-specific ESKD incidence rates are projected to stay relatively constant or decline, ESKD incidence and prevalence *counts* (numerators of the incidence rates and prevalence proportions) will continue to increase through 2030. The projected number of patients diagnosed with incident ESKD in 2030 is 137,000-151,000, a 19-32% increase from 2013, depending on obesity trends. The crude

(unadjusted) incidence rate will increase to 381-421 per million/year, a 5-16% increase. The projected number of patients with ESKD in 2030 is 794,000-1,219,000, a 22-88% increase, depending on trends in obesity and ESKD death rates through 2030. The point prevalence is expected to increase to 2,200-3,400 per million in 2030, an increase of 9-67%.

Conclusion

Though the increase in ESKD incidence within age groups has leveled off or tended to decline in recent years, aging and changes in the racial distribution of the population, changes in obesity and diabetes prevalence, and improved ESKD survival are expected to result in an increase in the overall (crude) incidence rate by 2030. The number of prevalent ESKD patients and the prevalence proportion are expected to increase through 2030 in all scenarios. Planning should account for these ESKD projections.

Introduction

In 2013, among patients with end-stage kidney disease (ESKD), defined in this study as those formally registered to receive maintenance dialysis or transplantation as renal replacement therapies, 79% had Medicare as either the primary (416,808 patients) or secondary (57,677 patients) payer.[107] ESKD patients represent 1% of the Medicare population, but account for 7% of Medicare's expenditures.[108]

Whenever a patient starts treatment for ESKD, CMS requires that their information be reported on the Medical Evidence Form (CMS Form 2728) for them to receive Medicare benefits. This information includes many patient factors, including demographics (e.g., age, race) and the primary cause of ESKD identified by the treating physician.

While the crude ESKD incidence rate has been increasing, the age-sex-race-adjusted incidence of ESKD has leveled off and declined since 2009.[109] This may be due, in part, to the decrease in age-specific incidence of ESKD attributed to diabetes.[110] On the other hand, Census projections based on declining death rates in the general population and changes in the racial demographics of the country estimate an aging, more racially diverse general population, which forms a growing at-risk pool of potential ESKD patients. The issue of what these trends mean for the ESKD population is of considerable interest since changes in ESKD trends have the potential for large impacts on resource allocation and costs.

Prior work developing projections of ESKD incidence and prevalence have employed methods insensitive to underlying changes in population and specific causes of incidence. One such paper successfully bracketed the actual 2000 ESKD prevalence by plotting both linear and exponential growth curves on data through 1997. [111] A more sophisticated model, using a stepwise autoregressive method with exponential smoothing came within 10% of the 2010 prevalence based on 1982-1997 data.[112].

The Gilbertson et al.[113] simulation model related the size of the diabetic and non-diabetic populations, both generated using linear projections, to project ESKD incidence and prevalence. They used CDC National Health Interview Survey (NHIS) data in a compartmental model with compartments defined by incidence, prevalence, diabetes status, and mortality over seven age groups, three race groups, and two diagnosis groups (diabetic and non-diabetic).This simulation model over-estimated the incidence rates and counts of the ESKD population after 2005.

We are using a simulation model that incorporates contemporary trends in population demographics, obesity, diabetes, and hypertension to more accurately project ESKD incidence and prevalence.[114] The projections could be affected by changes in the fundamental mechanism of ESKD incidence and risk-factor management. In order to limit this source of uncertainty, this work does not attempt to project these trends beyond 2030.

Methods

Simulation modeling approach

The current model has been described in chapter 3.[115] Briefly, we developed a compartmental model with compartments and flows (transition rates). After diabetes prevalence was estimated using various obesity projections in the first set of simulation models, the results were used in the ESKD simulation model as inputs, along with projections about general population size, hypertension prevalence, 'other' diagnosis ESKD incidence rates, and various ESKD death rate projections. Transition rates are modeled as constant within each year, but changing from year to year, with the restricted cubic spline estimate of trends over calendar years, with knots in 1988 and 1999, determined using Nelder-Mead optimization[116] (via the "optim" function in R[117]) on the sum of squared error in the incidence rates. . Simulations were constructed separately for the obesity-to-diabetes transition in the population, for diabetes ESKD incidence and for hypertensive ESKD incidence (i.e., new cases of ESKD with diabetes or hypertension listed as the primary cause on Form 2728). Uncertainty in projected population obesity or ESKD death rates was captured by showing the projections of ESKD incidence and prevalence associated with a wide range of projected inputs for each of these. Each of these was

simulated separately by age and race group. Programming for the simulation model was performed using the R v. 2.15.0 statistical package.[118]

Demographic categories

There are many population factors that influence projected trends in ESKD incidence and prevalence. Some factors identified as important in the literature include age, sex, race, BMI, ethnicity, and comorbid conditions such as hypertension and diabetes.[119] The age and racial distribution of the United States and the prevalences of obesity and diabetes are expected to continue to change in the near future; the overall proportionate distribution by sex is not expected to change as much. Our simulation model projections take these important factors into account by simulating each age and race group separately and combining the results.[120]

General population size estimation and projections

Census data for our analyses used US Census Statistical Abstracts of the United States,[121] and projections beyond 2010 were taken from US Census projections.[122,123] A weighted average was applied throughout each age/race group's estimates to smooth out rapid changes in count or trajectory, e.g., those due to changes in question format or sampling methodology in 2000.

Obesity prevalence and projections

There are indications that the increasing prevalence of obesity, defined as a body mass index (BMI) of 30 kg/m^2 or more, has started to level off. Ogden et al., for example, conclude

"Overall, there have been no significant changes in obesity prevalence in youth or adults between 2003-2004 and 2011-2012"[124]. There is an established progression of obesity to diabetes to kidney disease that makes obesity trends of particular interest when making predictions about the ESKD population.

For the simulation models, past obesity prevalence data were obtained from NHANES for each race and age group.[125,126] The two dashed lines in Figure 4.1 projecting the prevalence of obesity for the overall population are not intended to be specific predictions of future obesity prevalence. These projections deliberately represent an extreme range of plausible trends in the prevalence of obesity. This range was used to obtain the maximum influence that changes in obesity prevalence might have on the ESKD population. We expect that the actual obesity prevalence will lie between these two estimates. To simulate an obesity downturn, we used a quadratic regression fit based on the 1989 to 2012 data, which assumes that obesity prevalence has plateaued and will eventually fall. A linear regression fit over the same period was used to illustrate the assumption that there will be a continued rise in obesity prevalence. These projections were performed separately within each age and race group, and each simulation model was run under both assumptions-- quadratic and linear fit--to estimate the effects of these extreme projections on the sizes of the diabetes and ESKD populations.

Figure 4.1 also illustrates some of the dangers of using simple regression methods without data from the underlying at-risk population to extrapolate trends. Both projections are based on regressions, where $R^2 > 0.95$, yet they show very different projections of future obesity

prevalence. Since the purpose here was to create a wide range of estimates instead of a specific trend, however, this should not be an issue for this analysis.

Diabetes prevalence and projections

Our approach for modeling diabetes prevalence focused on predicting diabetes using the obese population. Obesity is a recognized risk factor for type 2 diabetes, is the most prevalent form of diabetes among adults.[127,128] Eighty percent of the adult population with diabetes is overweight or obese.[129] We used CDC NHIS data on the self-aware diabetic population to describe the population at most risk of ESKD with diabetes identified as the primary cause.

The transitions from obesity to diabetes and from diabetes to death were modeled as latent transition rate variables. The diabetes death rate was allowed to smoothly change over a period between 1991 and 2002 to reflect possible improvements in diabetes care; improvements on the death rates among people with diabetes around this period have been reported in the literature.[130] Projections were calculated based on simulated incidence and post-1996 death rates.

Hypertension prevalence and projections

Hypertension in NHANES was defined as having any of the following indicators: a systolic blood pressure (SBP) of 140 mmHg or greater, a diastolic blood pressure (DBP) of 90 mmHg or greater, or subject responses indicating that they were taking antihypertensive medicine, or had been diagnosed as having hypertension at least twice.

The prevalence of hypertension has not been increasing nearly as much as has the prevalence of obesity. Whites and blacks generally had a 2-5% increase in hypertension between 1988-94 and 2007-2012,[131] but this may have been due to aging. White median age increased from 32 in 1980 to 39 in 2000, and black median age increased from 25 to 30 over the same period.[132] Projections used linear regressions on recent past hypertension prevalence, resulting in a small increase of 2% overall, due more to demographic shifts (e.g. the aging population) than to progression within age/race groups.

ESKD incidence and subtype projections

ESKD incidence attributed to diabetes or hypertension

ESKD incidence was obtained from the USRDS RenDER system.[133] The incidence rates of ESKD for which the primary cause was attributed to diabetes or to hypertension were estimated each year since 2012 separately for each age-race group. In the simulation model, we used simulated estimates of diabetes prevalence in the general population based on both linear and quadratic obesity assumptions. Similarly, we used observed hypertension prevalence data along with linear extrapolations constructed within each age-race group.

ESKD incidence attributed to other causes

In 2013, the USRDS attributed 73% percent of all ESKD incidence to diabetes or hypertension as the primary cause.[134] The remaining ESKD subtypes were 'other' (9%), glomerulonephritis (8%), unknown/missing (7%), cystic kidney disease (2%), and other urologic diseases (1%). Linear regressions on the combined "other-cause" subtype of ESKD were used to project trends through 2030. The R^2 values for linear regression models were 0.96 for most ESKD subtypes based on 1985-2013 data and for the glomerulonephritis and "other/missing"

subtypes based on 1999-2013 data. In other linear models, the R^2 value was 0.84 for the cystic-kidney–disease subtype and 0.67 for urologic-disease subtype.

ESKD death projections

ESKD death rates were obtained from the USRDS RenDER system.[135] The death rate among ESKD patients has decreased over the past two decades, both overall and within specific age groups.[136] These temporal trends ranged from a 1.4%/year proportional decrease in the death rate for white patients over age 75 years to a 2.4%/year proportional decrease for white patients ages 45-64. As with the obesity projections, we did not rely on a single projected ESKD death rate trend. We ran models first assuming that the current downward trend continues unabated, and then assuming that the current death rate remained constant throughout the simulation, as illustrated in Figure 4.2, which shows both projections for each age group.

Population movement and loss to follow-up

While data are supposed to be reported for all US ESKD patients, some (<1%) are lost to follow-up each year. The net gains and losses from each age/race group, were projected using a linear model attenuating the slope over time. This attenuated slope projection method has proven successful in other research areas; e.g. attempts to project cancer incidence.[137]

Results

Diabetes prevalence projections

Despite the fact that, depending on the year, up to 65% of the patients with type 2 diabetes were not obese at the time of their ESKD diagnosis, the use of obesity data to predict trends in the empirical data seemed to result in simulated results fairly consistent with observed results through 2014.

Figure 4.3 shows the annual prevalence (%) of diabetes from 1980 to 2030, by race (5A) and age (5B), based on two assumptions regarding the projected trend in obesity prevalence after 2012 (as illustrated in Figure 4.1) as a percentage of the population. Generally, diabetes prevalence is expected to be greater in 2030 than it is today for both whites and for blacks. Among whites, we expect the current prevalence of approximately 7% to increase to between 9-12% by 2030, depending on the obesity trajectory. Similarly, among blacks, we expect the prevalence to increase from approximately 9% to between 16-18%. Overall, the diabetes prevalence will be between 11-13%.

Diabetes prevalence is also expected to increase for most age groups, although the obesity projections have more of an effect on the older age-group projections where diabetes is more common. Diabetes prevalence is expected to be approximately 2% among adults under age 45, 17-21% for those 45-64, 26-31% for those 65-74, and 19-26% for those over age 75. Diabetes prevalence among younger populations did not decrease despite any projected decrease in obesity; only the oldest group (75+) seemed to experience a decline.

ESKD Incidence projections

ESKD incidence was modeled separately for diabetes, hypertension, and other ESKD subtypes for each age and race category. The results were computed for each of the obesity projections and then combined by age category and by race. Generally, the incidence rates that are calculated separately for age and race groups and then summed are increasing, albeit at a rate far slower than the increase before 1995.

Figure 4.4a shows the annual ESKD incidence rate from 1980 to 2030 by race with two simulated projections after 2013, based on different projections of obesity prevalence, and using three race groups (white, black, other) and NHANES obesity data. ESKD incidence continues to be lower for whites than for blacks. The projected incidence rate for whites rises from 317 per million/year in 2013 to between 363 and 391 per million/year by 2030, depending on the obesity trajectory. The projected incidence rates for blacks rise from733 to between 751 and 817 per million/year by 2030. The projected incidence rate for other races fall from 227 per million/year in 2013 to between 148 and 162 per million/year in 2030. Incidence rates for other races started dropping sharply around 2000, which is when this category sharply increased in size on the census (the denominator), possibly due to changes in the census data collection method. Overall, the incidence rate is projected to rise from 363 per million/year in 2013 to between 389 to 424 per million/year in 2030.

Figure 4.4b shows the annual ESKD incidence rate from 1980 to 2030 by age. The ESKD incidence rate was greater for adults over age 65, especially after the late 1980s. The temporal trend was projected to be rather flat, albeit declining somewhat for those under age 45, from 75

per million/year in 2013 to 60-63 per million/year in 2030. The decline was projected to be similar for those aged 45-64, at 537 per million/year in 2013 and 488-518 per million/year in 2030. There was a decline in the projected incidence for those aged 65-74, from 1151 per million/year in 2013 to 1016-1104 per million/year in 2030. The rate among those aged 75 and over was more variable. The simulation model did not predict the sudden decrease between 2010-2013 from 1518 to 1391 per million/year. If we assume that the sudden decrease represents random variation, and that the 'true' rate is closer to the modeled rate of 1516 per million/year in 2013, then there is no clear indication of a trend upwards or downwards. The2030 incidence is projected to be 1370-1509 per million/year.

ESKD prevalence projections

ESKD death-rate projections were combined with ESKD incidence projections (shown in Figure 4.4) to estimate the trend in ESKD prevalence. The increasing incidence rate along with the increasing size of the United States population and the constant or decreasing modeled ESKD death rates mean that the number of prevalent ESKD cases is projected to continue to increase after 2012.

Annual ESKD prevalence per million population are shown by race (figure 4.5) and by age (figure 4.6). Each figure shows results from each of the four scenarios representing different assumptions about obesity and ESKD death-rate trends after 2013: a) linearly increasing obesity prevalence and a constant ESKD death rate; b) linearly increasing obesity prevalence and a proportionately dropping ESKD death rate; c) a quadratic obesity prevalence leading to an

eventual decrease in obesity and a constant ESKD death rate; and d) a quadratic downturn in obesity prevalence and a proportionately decreasing ESKD death rate. The prevalence is projected to rise 18-50% for whites, 5-28% for non-whites, and 15-43% overall in 2030 compared to 2012. For those adults under 45, the prevalence is expected to drop 25-30%. The prevalence of ESKD is expected to rise 3-25% for adults 45-64 and 25-65% for those 65-74. For those over 74, the prevalence is expected to increase between 8% and 43%, depending upon the scenario.

Since the size of the population is increasing, the counts of ESKD patients (not shown) are projected to rise even more sharply than the prevalence proportions. ESKD prevalent counts are projected to increase by 4-25% through 2030 for ages 45-64, 103%-169% for ages 65-74, and 63%-109% for ages 75 and older. The decrease in incidence for those aged less than 45 is projected to result in a 19-25% decrease in the prevalent count for this group. The size of the entire ESKD population is projected to increase 28-47%. In each scenario, the prevalent count of ESKD patients is projected to continue to increase through 2030 for white patients, non-white patients, and overall.

The projected number of prevalent ESKD patients varies much more with the different assumptions about the future trend in the ESKD death rate than the future trend in obesity prevalence. The differing obesity projections changed the 2030 prevalent count by about 34,000-39,000 patients, whereas the differing death-rate projections varied the 2030 prevalence count by about 158,000-163,000 patients.

Figure 4.7 summarizes the results of the different simulation runs and sensitivity analyses. The simulations using three racial groups (black, white, other) within each age/diagnosis group generated slightly higher estimates than did the simulations using two racial groups (white, non-white). The three-race simulations exhibited much more instability, especially in the smaller cells (e.g., 75+, other racial group). We cannot determine whether the larger estimates represent improved accuracy due to including more specific patient categories in the simulation models or unstable estimates due to smaller cells.

Discussion

Despite the steady or decreasing age-specific incidence rates of ESKD projected through 2030, possibly due to improvements in care, the annual number of incident cases and the crude incidence rate of ESKD are projected to increase in the U.S. during that period. Similarly, the number of prevalent cases and crude prevalence of ESKD are also projected to increase through 2030.

The results from the simulations shown in Figure 4.7 indicate increases in incidence across the various assumptions. This overall increase in ESKD incidence rate is projected to be between 5% (rising to 381 per million/year in 2030 v. 363 per million/year in 2013) and 16% (rising to 421 per million/year in 2030), depending on obesity trends and racial groupings. Incident counts are expected to increase to 137,000-151,000 per year, a 19-32% increase over the 2013 incident count of 115,042. ESKD prevalence is expected to increase to between 2200-3400 per million, an increase of 9-67% over the 2013 prevalence of 2034 per million. The number of ESKD prevalent cases is projected to continue to increase to somewhere between 794,000 and

1,219,000 patients by 2030, an increase of 22-88% over the 2013 prevalent count of 649,538 ESKD patients. The differing obesity projections varied the 2030 prevalent count by 39,000-47,000 patients, an ESKD prevalence proportion of 109-131 per million. The differing death-rate projections varied the 2030 prevalent count by 283,000-291,000 patients, or an ESKD prevalence proportion of 787-810 per million. Constant death rate projections (green bars) yielded lower prevalent counts and prevalence proportions (per million) than decreasing death-rate projections (blue bars). While we cannot predict the overall impact of future developments in ESKD treatment on patient survival, we expect that the projected trends based on assumed continued improvement are likely to be closer to the truth than projections based on constant death rates.

The increasing age-sex-race-adjusted incidence rate of ESKD leveled off after 2001, then declined after 2006. [138] As the population continues to age and grow more racially diverse, as projected by the US Census Bureau, the increased number of older people will offset the decreasing within-age-group trend shown in figure 4.4b, resulting in an increasing crude (unadjusted) incidence rate of ESKD.[139] These projections are continuations of recent trends, where age-specific incidence rates have declined, while the crude incidence has increased in the US[140] and in Japan.[141] Those recent results are very consistent with the projections in this paper, which project steady or declining incidence rates within specific age groups, but an increase in the overall incidence rate of ESKD. Note that in Japan, data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) suggests that the age of the hemodialysis patients may be increasing more rapidly than in the US, which would exacerbate these trends.

Another consequence of the aging general population is an aging ESKD population. Figure 4.8 projects the age distribution of the ESKD population into the future, showing an increase in the proportion of ESKD patients over age 65. In 2013,approximately 40% of the population was older than 65. In 2030, we project that this proportion will increase to 55-61%, depending mainly on whether the death rate continues to decline (61%) or remain constant (55-56%). The aging ESKD population will likely impact types of care for the dialysis population, resulting in increases in the resources required for the dialysis population beyond the increases indicated by the strict numerical increases. While the patient count is expected to increase up to 88% by 2030, the cost to Medicare, already exceeding $30 billion/year, may grow well beyond this percentage increase due to the complications associated with caring for an increasingly older population, unless costs per patient are somehow reduced.

Gilbertson et al. (2005) predicted 120,000 (105,000-135,000k) incident ESKD patients and 591,000 (534,000-647,000) prevalent ESKD patients in 2010; the actual numbers were slightly lower, albeit within the 95% confidence intervals: 113,000 incident cases and 587,000 prevalent cases. During 2010-2015, the Gilbertson et al. counts were progressively less accurate, projecting increases well beyond the actual trend. For example, Gilbertson predicted approximately 130,000 incident patients in 2013; the actual number was 115,000. One possible explanation for this difference lies in changes in patient treatment that were not adequately captured by Gilbertson's linear extrapolations of diabetic incidence rates. For example, it is possible that better prevention or management of diabetic kidney disease through blood pressure control, glucose control, and RASi use have had an effect on ESKD incidence. Landmark clinical trials (HOPE[142], DCCT[143], RENAAL[144]) showed that these treatments substantially

delayed onset of renal disease outcomes among patients with diabetes. [145,146,147] Another difference between this work and the earlier work by Gilbertson et al. may be improved demographic definitions and projections. We show that the demographic changes, such as the aging population, will increase ESKD incidence, but we also show that age- and race-specific ESKD incidence may be decreasing, partially countering the demographic effect.

The current analyses do not present confidence intervals for data within individual years or for the projections. Confidence intervals are used to estimate the probable range of results from identical samples drawn from a single source population, not for estimates of the population as a whole. While the USRDS probably misses some cases of ESKD, the fact that ESKD patients are required by law to be registered so Medicare payment can be arranged means that relatively few patients are omitted. Confidence intervals for the estimated projections based on the simulation models containing over two million patients with incident ESKD over the years are unrealistically narrow, and the use of the entire US ESKD population means that statistical techniques based on sampling are not valid. We feel that the range of estimates based on the varying input assumptions shows the accuracy or uncertainty of these projections in a way that is much more theoretically and practically justifiable.

Within age/race groups, death rates have decreased by 1.4%-2.4% per year since 1985 in the ESKD population. This will result in a continued increase in the prevalence of ESKD unless incidence declines sharply. Given the aging population and the increasing prevalence of diabetes and hypertension, this seems unlikely.

As the population continues to age, we expect to see an expansion of the resources needed for chronic disease care in general and for the diabetes and ESKD populations in particular over the next few decades.

Limitations

Whenever we attempt to forecast ESKD prevalence in a population for more than a decade, regardless of the method, it is difficult to capture the level of uncertainty arising from many assumptions. The current simulation assumes that the current trends in the population and in the process of transitioning to ESKD continue for each of the components. For example, this paper assumes that the declining trend in diabetic ESKD incidence, possibly due to improvements in the prevention and treatment of diabetic kidney disease, will continue through 2030. The current analyses also assume that recent improvements in care for the general population, the obese, people with diabetes, people with hypertension, chronic kidney disease patients, and ESKD patients will continue smoothly through 2030. These treatments can have opposite effects in ESKD prevalence. For example, helping diabetes patients avoid renal microvascular events can prevent or slow their progression to ESKD, but these treatments can also prevent cardiovascular events, keeping these patients alive long enough to develop ESKD. While we attempted to portray the effects of reasonably wide ranges of future trends in obesity and ESKD care, major changes in the treatment among any of these populations (e.g. genetic treatments lowering ESKD incidence among populations with the APOL1 gene) will have cascading effects through the entire system that will not be reflected in the current analyses, although these effects would have to be extreme in order to substantially impact the ESKD population by 2030.

The fact that, as this manuscript demonstrates, current trends are likely to lead to massive increases in the size of the ESKD population points to the imperative to develop new treatment options that will hopefully render these projections invalid. For example, new treatments based on APOL1 research could result in substantially reduced racial disparities in ESKD incidence. Due to population trends in the US racial composition, this could potentially have substantial impacts on the size of the overall ESKD prevalent population in the future. Similarly, the have been a number of SGLT2i studies showing promising results in terms of slowing progression to kidney disease endpoints, preventing albuminuria and/or substantial reduction in kidney function, as measured by the eGFR (estimated glomerular filtration rate).[148] These treatments in clinical trials that could either continue current trends in decreasing age-category-specific ESKD incidence among patients with diabetes, which would be in line with the projections used in this manuscript. Alternatively, they may alter the trajectory of ESKD incidence much more radically, which would mean that the simulation would end up over-estimating ESKD incidence among diabetics. Similarly, if the recent decrease in incidence among the population over age 75 is real, and not random variation, then our simulation will over-estimate the incidence, and thus the prevalence of ESKD to some extent.

The best option is to prevent patients from reaching ESKD in the first place, but realistically we will also need alternative treatments that will both improve patient outcomes and reduce the resources needed for the ESKD population. In-center dialysis is one of the more expensive options for ESKD care in the long term.[149] We need to continue to develop innovative, patient-centered approaches that provide more options in order to continue providing the needed

care for these patients. Recent improvements in transplantation allocation have helped reduce racial disparities and are likely to produce better results for the people transplanted.[150,151] Work is progressing on alternatives to dialysis and donated organ transplantation, including wearable artificial kidneys and bioartificial kidneys. Patient survival and other outcomes are generally better with a transplant compared with dialysis,[152] and increasing use of these options would reduce the overall resources needed to care for this population.

Another alternative treatment for people with ESKD is conservative management, i.e., managing symptoms without renal replacement therapy (dialysis or transplantation). Rose et al.[153] argued that the population facing ESKD, particularly the frail elderly, is choosing conservative management more frequently over time, although accurate counts are not yet available. The current simulation model naturally incorporates the effects of recent trends in this treatment on incidence rates. However, if conservative management should substantially increase over time, the projections for treated ESKD incidence (dialysis or transplant) will be lower than our projections shown in the figures, and death rates among ESKD patients would also be expected to be lower than current projections. Future simulation modelers of ESKD trends may be able to obtain the data needed to address trends in conservative management as a separate category of treatment.

Conclusions

The aging population, increasing racial diversity, rising prevalence of comorbid conditions such as diabetes and hypertension, and decreasing ESKD death rates (e.g. due to improved treatment of ESKD patients) have made an increasing prevalence of ESKD in the U.S.

population very likely, even with future improvements in slowing CKD progression to ESKD. Based on the findings of our simulations, any plans for ESKD resource allocation should allow for substantial continued ESKD growth in the size of the prevalent patient population through 2030. This has strong implications for planning of dialysis infrastructure (dialysis facilities, provisions for home hemodialysis, increased peritoneal dialysis use, etc.), and Medicare and Medicaid budgeting. We need to continue developing innovative approaches to prevent ESKD and to care for ESKD patients to cover this growing need.

Acknowledgment

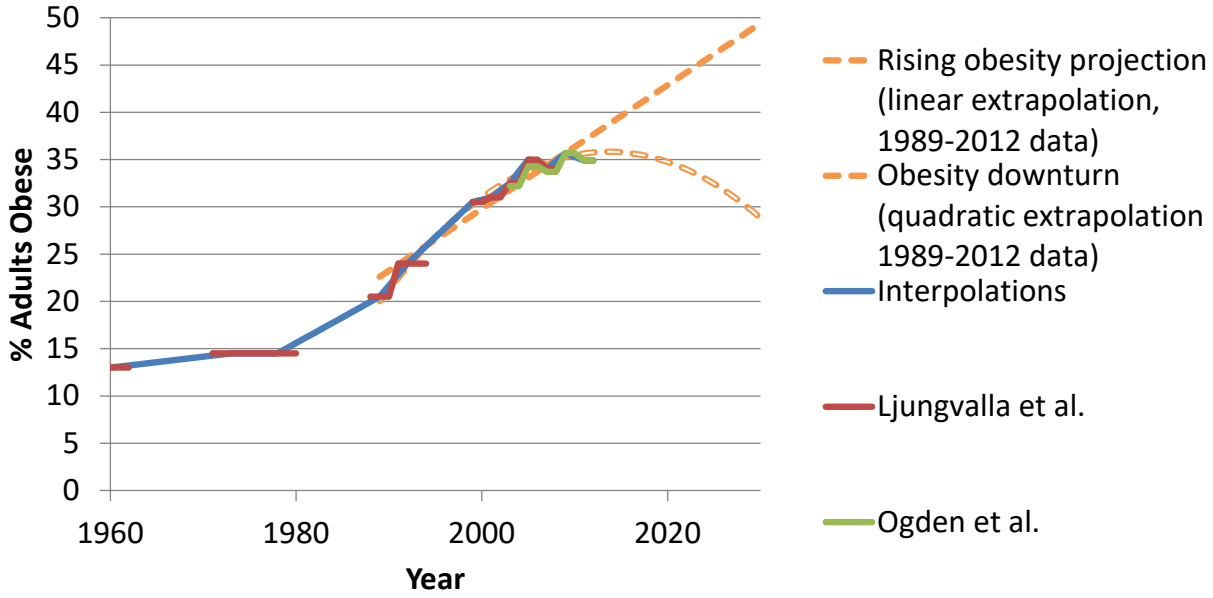
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Disclaimer

Some of the data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the U.S. government.

Figures

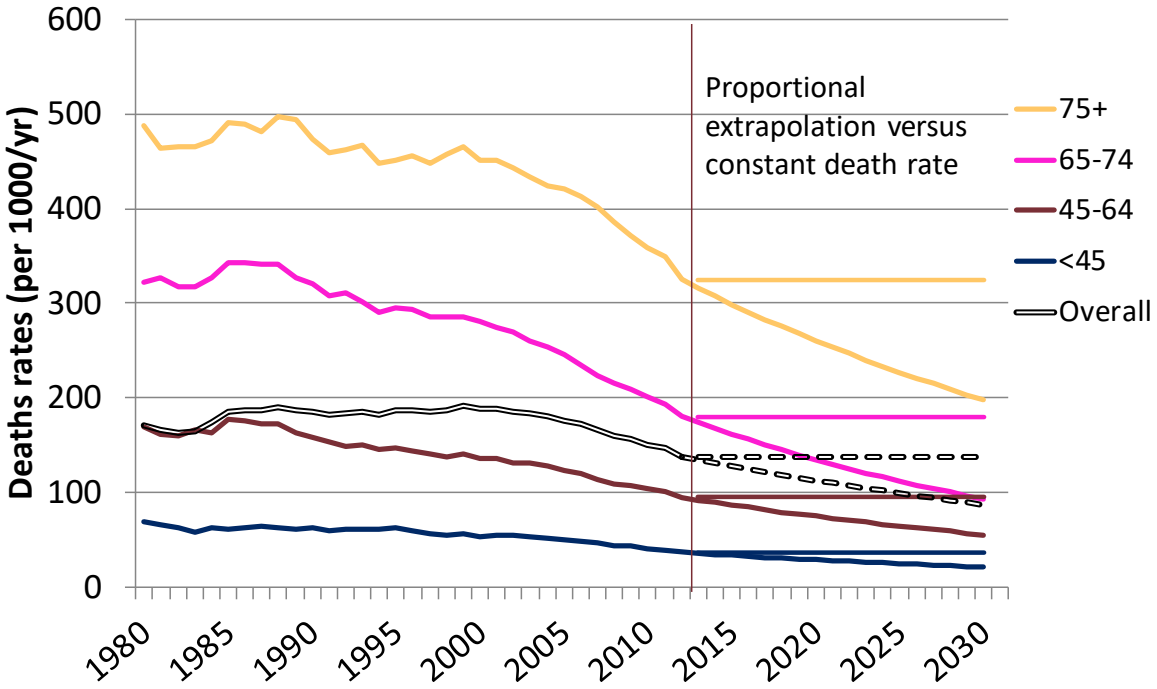
Figure 4.1: Estimated and projected trend in the prevalence of obesity (BMI 30+ kg/m^2) (%) between 1960 and 2030 in the general U.S. population.



Quadratic regression $R^2 = 0.99$, linear regression $R^2 = 0.95$.

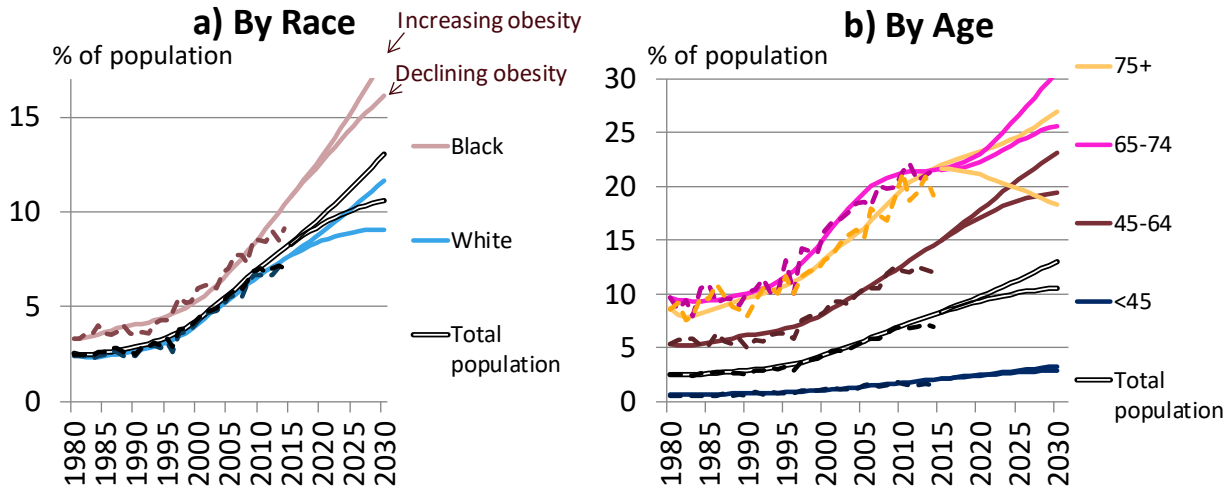
Legend: Estimated obesity prevalence from Ljungvalla et al. (2012), Ogden et al. (2014), using NHANES data.

Figure 4.2: Age-specific ESKD death rates (per 1000/year), by year (1980-2030), with two projections after 2012 (proportional decrease and constant death rate)



Legend: 1980-2013 data from USRDS RenDER,[154] with extrapolations after 2012 based on proportional decrease in death rates and constant death rates.

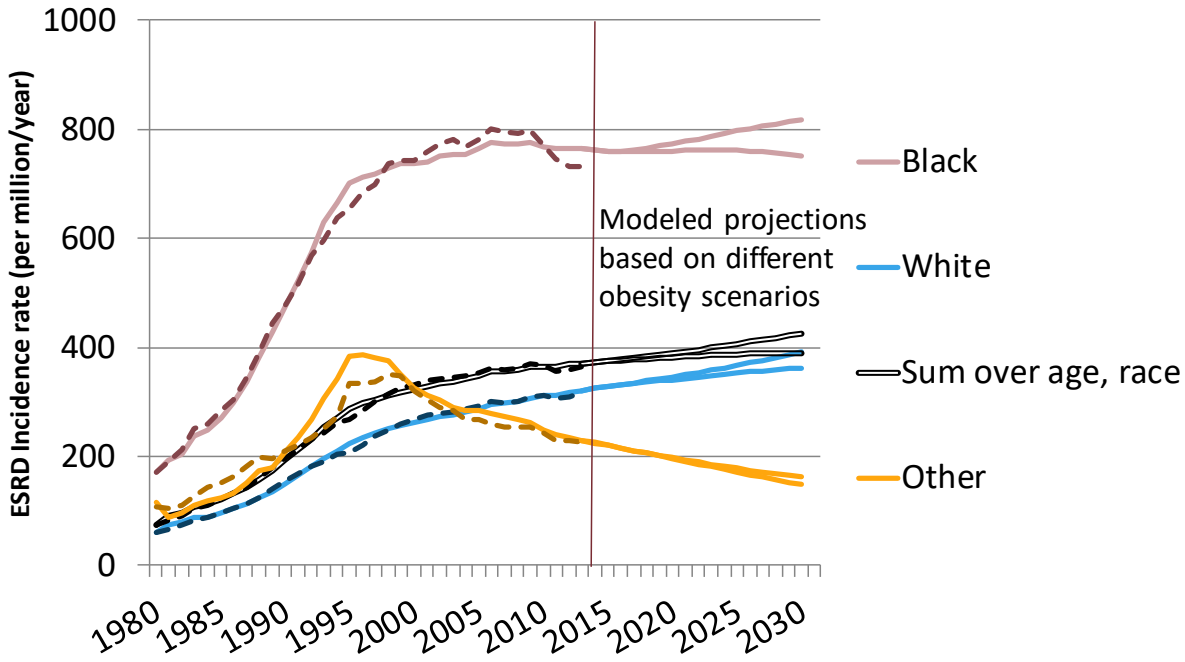
Figure 4.3: Annual diabetes prevalence from 1980 to 2030, by race (a) and age (b), with two assumptions about the projected trend in obesity prevalence after 2012.



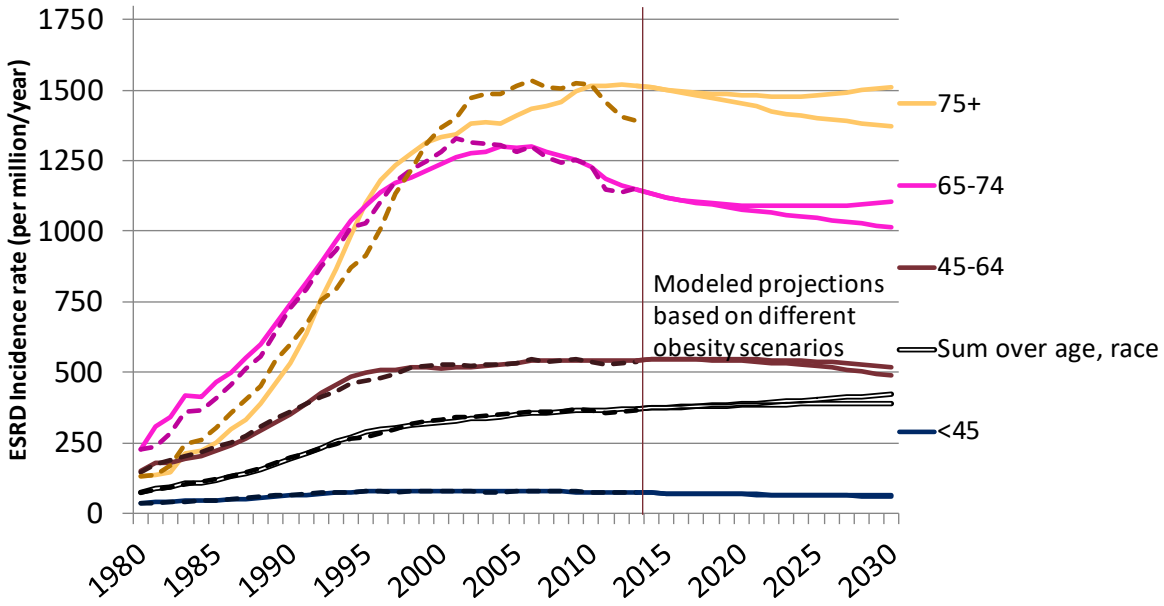
Legend: Dashed lines represent reported data, solid lines represent simulated data. Reported data on diabetes prevalence from the CDC NHIS.[155] Simulation results are based on increasing obesity trend versus decreasing obesity projections.

Figure 4.4: Annual ESKD Incidence rate (per million/year) from 1980 to 2030 by (a) race and (b) age, with two assumptions about the projected trend in obesity prevalence after 2012

(a) ESKD incidence by race group and obesity assumption

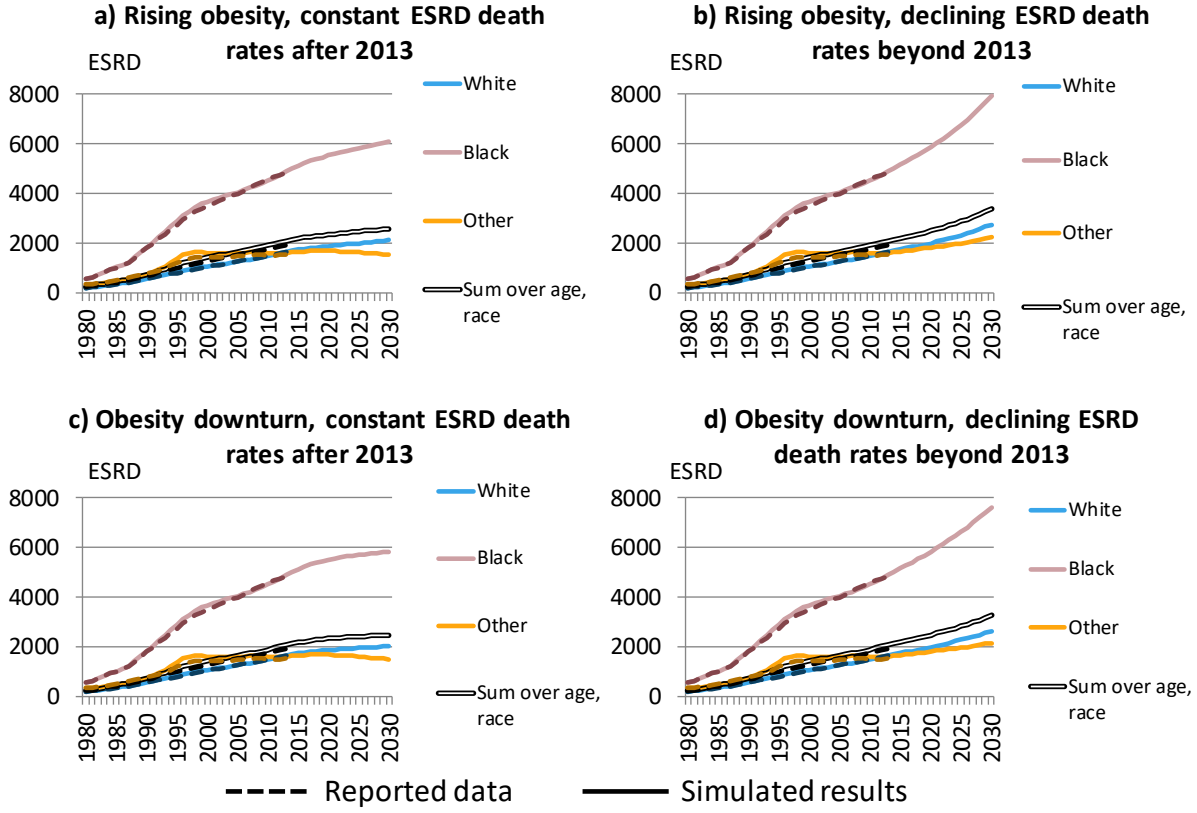


(b) ESKD incidence by age group and obesity assumption



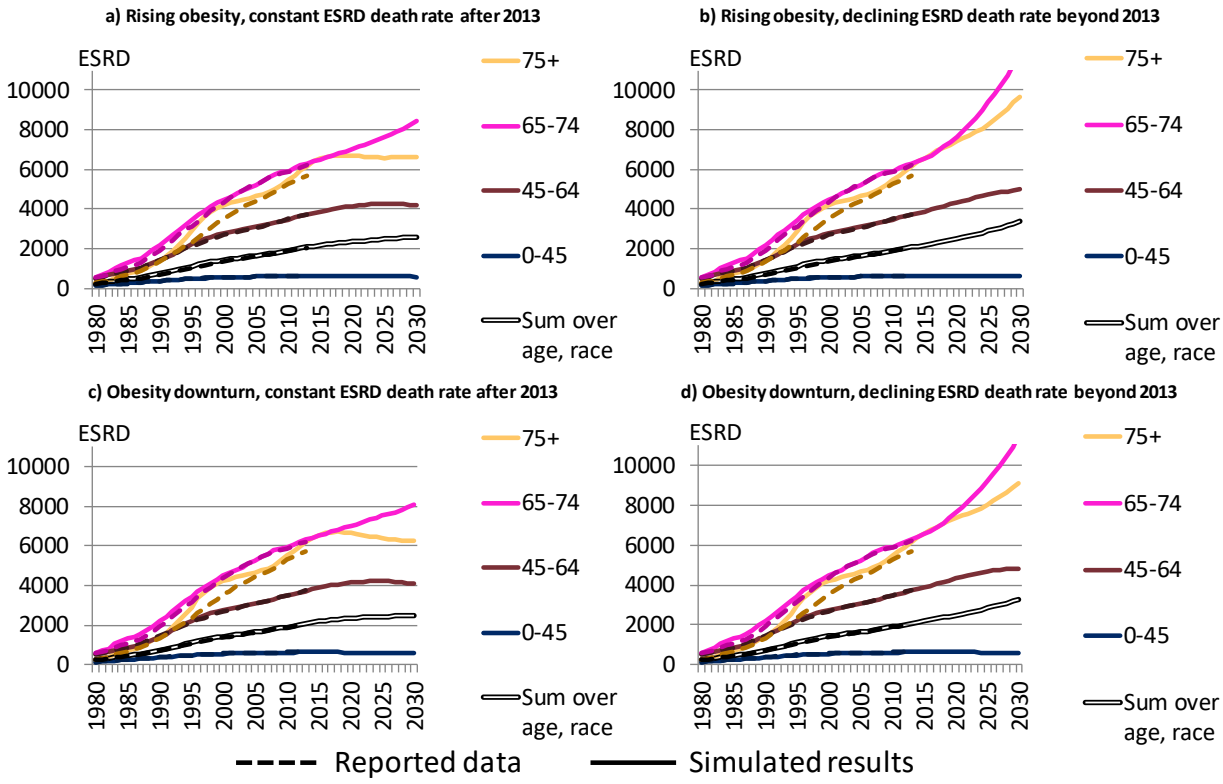
Legend: Dashed lines represent reported data, solid lines represent simulated data. Incident counts from USRDS RenDER system,[156] accessed January, 2016. Population counts from smoothed CDC-bridged US census data. Simulation results are based on increasing obesity trend versus decreasing obesity projections.

Figure 4.5: ESKD prevalence proportion (per million) by assumptions of obesity and ESKD death-rate trends after 2012 (a-d), age/race group (color coded), and year (observed [dashed curves] and simulated through 2012; projected after 2012 [solid curves])



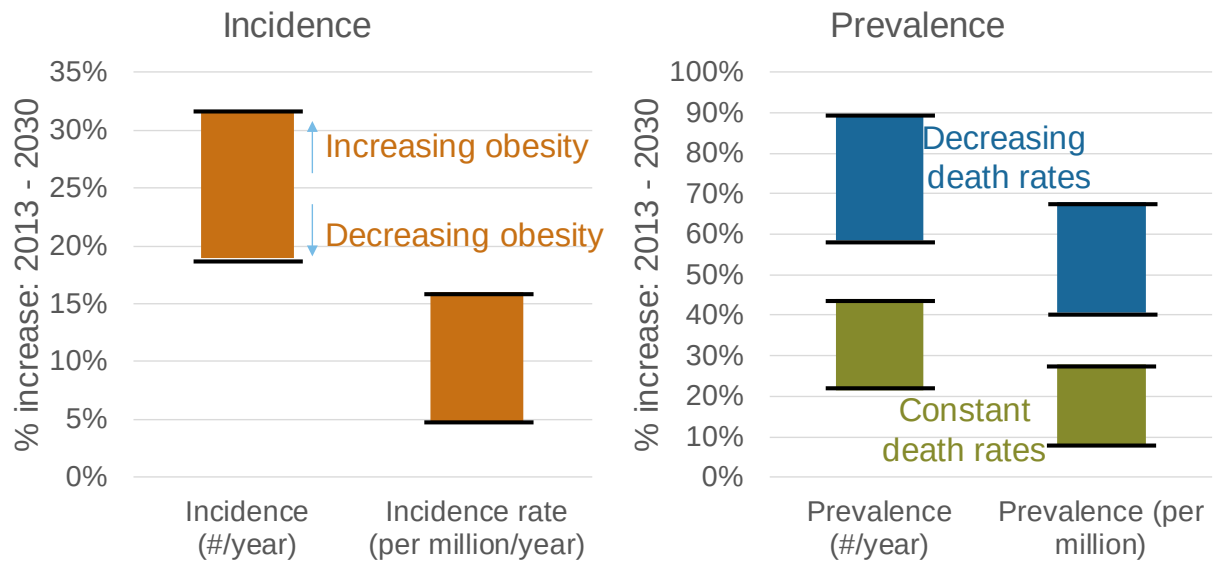
Legend: 1980-2012 ESKD prevalent counts from USRDS RenDER.[157] Population data from smoothed, CDC bridged US Census data. Simulation results are based on increasing obesity trend versus decreasing obesity projections and constant ESKD death rate versus continued proportional decrease.

Figure 4.6: ESKD prevalence proportion (per million) by assumptions of obesity and ESKD death-rate trends after 2012 (a-d), age group (color coded), and year (observed [dashed curves] and simulated through 2012; projected after 2012 [solid curves])



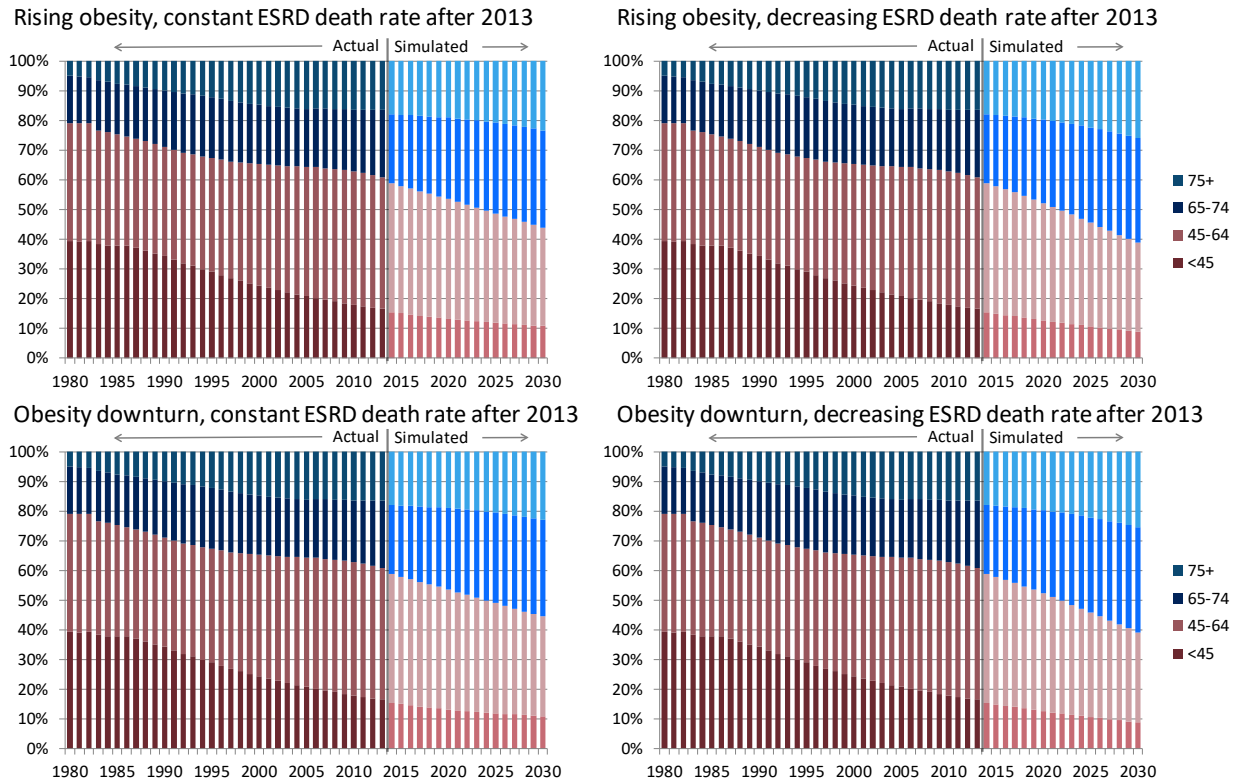
Legend: 1980-2012 ESKD prevalent counts from USRDS RenDER.[158] Population data from smoothed, CDC bridged US Census data. Simulation results are based on increasing obesity trend versus decreasing obesity projections and constant ESKD death rate versus continued proportional decrease.

Figure 4.7: Ranges of simulatedsincreases in incidenceincidence counts and rates, and prevalence and prevalence counts, between 2013 and 2030, based on various assumptions about obesity and ESRD death rates and sensitivity analyses



Legend: Ranges of simulation results over varying assumptions and methodologies. Each bar represents the range of six results across simulations assuming increasing obesity v. decreasing obesity, each over three methodologies: two racial categories (white/non-white) and proportional obesity hypertension rates across race groups, two racial categories and NHANES obesity and hypertension rates, and three racial categories (white/black/other) and NHANES obesity and hypertension rates. Separate bars are shown for the prevalence under differing assumptions about the ESKD death rates (constant v. decreasing death rates).

Figure 4.8: Age distribution of prevalent ESKD patients, by obesity assumption and death rate assumption



Legend: Simulation based on three race groups (black/white/other), NHANES data on obesity.

Chapter 5 Conclusion

Case-mix-adjusted survival among hemodialysis patients has been improving in Europe, Japan, and the United States. Improvements in dialysis practice measures appear to explain substantial proportions of these improvements. The specific improvements that contributed the most for each region are not identical. Among adult hemodialysis patients, age adjusted survival has improved by 24% per decade in Europe, 9% in Japan, and 45% in the US. Changes in practice measures may explain as much as 17% longer survival per decade in Europe, primarily through Kt/V and phosphorous control. Improvements in Kt/V and Inter-Dialytic Weight Gain (IDWG) can explain 10% longer survival per decade in Japan. Fistula use and phosphorous control primarily explain the 26% per decade improvement in patient survival in the United States.

In the United States, improved ESKD patient survival is one of the factors helping drive increasing ESKD population prevalence. Other contributing factors include the aging population, increasing obesity, and changing population racial demographics. These trends are expected to result in increasing crude ESKD incidence rates and prevalence through 2030. Incidence rates within age groups have leveled off or tended to decline, suggesting better management, but this trend is not enough to offset the factors driving the increasing trends in the numbers of new and existing cases of ESKD. Differing obesity projections have relatively little effect on diabetes incidence and ESKD incidence through 2030. As shown in Figure 4.7, the number of patients

with ESKD is expected to increase 22-88% to from 649,538 in 2013 to 821,000 - 1,220,000 by 2030.

We hope that an improved understanding of past achievements in patient survival will help us to continue trends in improved patient survival. While progress has clearly been made in the measures studied, there is still room for improvement. There are substantial between-region differences in some of the measures, indicating areas where improvements can continue. In addition, there is no reason to believe that the current set of recommendations cannot be improved by future research. Future practice recommendations may be more specific, cover more areas of patient care, and be more specific to the needs of individual patients, and these improvements may help continue current trends in improved patient outcomes.

Caring for ESKD patients using the best, evidence-based practices is only the first step. If patient survival continues to improve, and if current demographic trends continue as expected, then there will be substantial growth in the prevalent ESKD patient population. If we are to continue to provide high-quality care for these patients, we will need to continue to develop innovative and effective ways to prevent and/or treat ESKD, and those involved in planning national and local resource allocation will need to incorporate this growth into their planning. We can continue to improve the lives of ESKD patients if we combine scientific evidence and expert judgment into procedures and planning to meet their current and likely future needs.

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