Supplemental materials

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Supplemental Appendix 1: *Simulation modeling approach*

ESRD incidence was modeled in separately depending on whether it was diagnosed as caused by diabetes, hypertension, or other causes. Within each diagnosis group, the models were calculated separately within each age and race category. The results were combined for overall estimates and for race- and age-specific reporting.

Figure 3 shows the annual ESRD incidence rate from 1980 to 2013 by age group. The ESRD 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.

The incidence rates by age and by race obtained through simulation modeling seem to be ranked among the demographic groups and diagnoses in a manner consistent with the relative rates reported in the published literature. The simulations matched data from other sources that show higher incidence for blacks and greater increases in ESRD incidence since 1980 in the older population.[1]

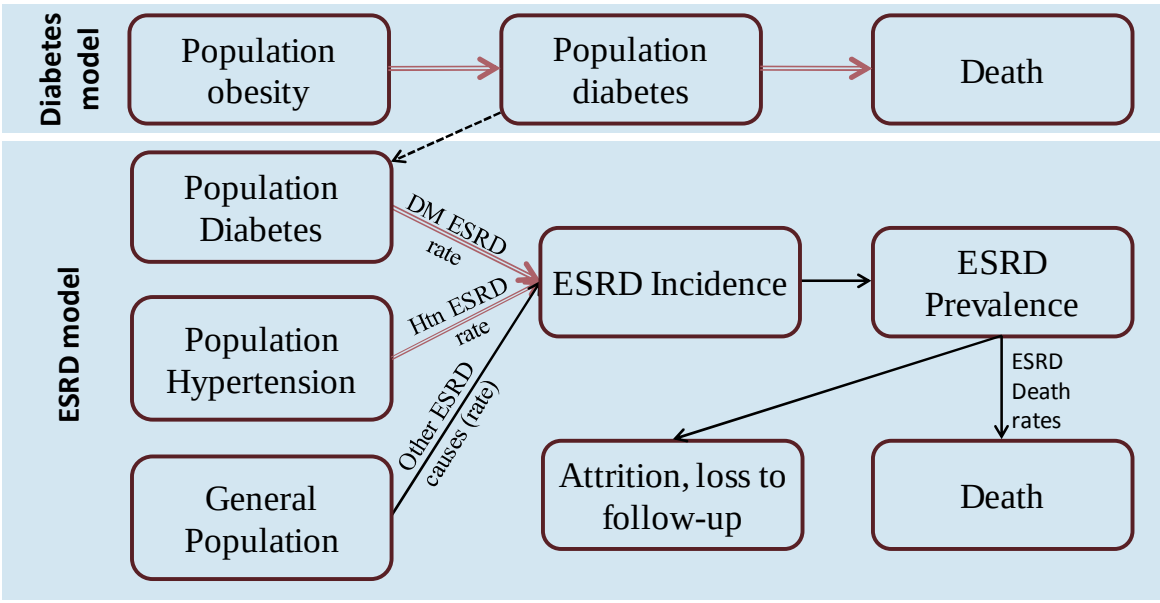
Attempts at validation using earlier periods to predict known 2015 data tend to over-estimate current incidence for much the same reason as the Gilbertson et al. simulation model did: the earlier data do not adequately reflect the downturn in diabetes incidence. We used data through the year 2000 to estimate incidence in 2013 and showed a result of roughly 144,000 incident patients/year, which was higher than the Gilbertson et al. result of 136,000. The actual incidence rate in 2013 was 118,160.[2] We acknowledge that substantial changes to the treatment of ESRD patients would render the current projections inaccurate as well.

Detail on the compartmental model

ESRD death-rate estimates were combined with ESRD incidence estimates (as shown in Supplemental Figure s1) to estimate trends in ESRD prevalence. The increasing incidence rate

along with the increasing size of the United States population and the generally decreasing age-specific ESRD death rates mean that the number of prevalent ESRD cases generally increased throughout the simulation period.

Supplemental Figure s1: 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

Equations for compartmental model

Each "compartment" in the compartmental model shown in figure 2 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.[3]
- 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"

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

- $\lambda_{RCS\text{-}ESRD\{diabetes,\ hypertension\}}$ (DG): Represents terms used in restricted cubic spline (RCS) for the rate of transition from source{cause} to ESRD per year
- $\gamma_{ESRD\{other\}}$(DG) = Other cause (non-hypertension, non-diabetes) transition rate
- γ_{Dth}(DG) = Transition from ESRD to death. Note that death rates are not calculated for each individual cause.
- $\gamma_{emigration}$(DG) = Transition from ESRD 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 ESRD 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.

The compartmental model has been used successfully in the past for chronic disease.[4] In this simulation, the compartments and flows (transition rates) used in each of the simulation models are diagrammed in Supplemental Figure s1. After diabetes prevalence was estimated using obesity and demographic data in the diabetes simulation model (see Supplemental Appendix 5: *Diabetes*), the results were used in the ESRD simulation model as inputs, along with general population size, hypertension prevalence, 'other' diagnosis ESRD incidence rates, and the remaining ESRD data. The outputs of the ESRD simulation model include ESRD incidence, prevalence, and deaths for each year for each demographic and diagnosis group of patients.

Transition rates to ESRD were allowed to change from year to year. Nelder-Mead optimization[5] (via the "optim" function in R[6]) was used on the sum of squared error in the incidence rates to obtain the estimated rates and their trends over time via restricted cubic splines. Knots at 1988 and 1999 were chosen based on the fit of the overall simulation model. Simulations for the obesity-to-diabetes transition in the population were constructed separately, and the results used for ESRD incidence with the primary causes identified as diabetes. Each of these simulations was modeled separately by age-race group, with separate rates calculated within each group. Incidence due to diabetes, hypertension, and other causes were each handled separately for each age and race 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 ESRD.

Supplemental appendix 2: Discussion of confidence intervals around population estimates

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 ESRD, the fact that ESRD 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 ESRD over the years are unrealistically narrow, and the use of the entire US ESRD 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.

Supplemental appendix 3: *ESRD demographics*

Some factors identified as important in previous literature include age (adjusted hazard ratio [HR] of ESRD 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). [7,8]

While ideally we would consider all individual risk factors for ESRD, 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 racial and ethnic categories have changed over time.

Supplemental Appendix 4: *CMS ESRD reporting requirements*

Whenever a patient starts treatment for ESRD, CMS requires that their information be reported on the Medical Evidence Form (CMS Form 2728) for them to receive Medicare benefits. The current (as of 2018) version of this form includes patient factors such as sex,

ethnicity (Hispanic/Latino), race (White, Asian, Black/African American, Native Hawaiian or Other Pacific Islander, American Indian/Alaska Native), the primary cause of ESRD identified by the treating physician, and several other factors. Many of the fields on the form have undergone revisions over the years; for example, in 2015 the cause of ESRD field was updated to use ICD-10-CM codes. Since 1995, this form has been required for all patients, not just Medicare-eligible patients. Patients with acute kidney failure who recover without a 2728 form being submitted are excluded from these analyses. Patients who recover permanently or who were lost to follow-up due to emigration were handled by a parameter estimated as a proportion (usually quite low) of the group being simulated, which was allowed to change over time.

There is also requirement that patients with ESRD who die will have the CMS form 2746 filled out by the dialysis or transplant provider within 30 days of death. This form identifies 90% of the ESRD population deaths. To supplement this information, the USRDS uses additional death information as detailed in the ESRD analytical methods section of their annual data report.[9]

Supplemental Appendix 5: *Diabetes*

Supplemental Figure s2 shows the annual point prevalence of diabetes on December 31 of each year from 1980 to 2013, by each age group within each race category, 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.

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

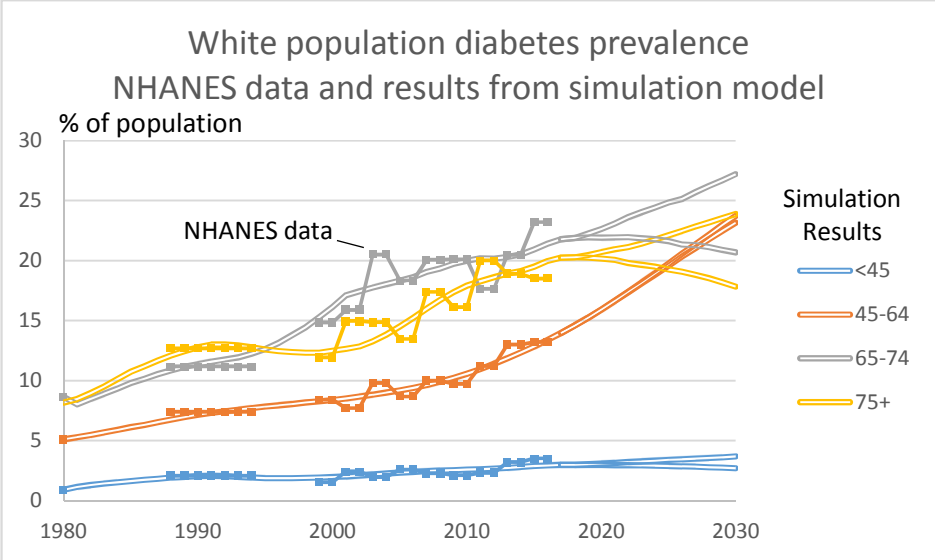
had higher incidence rates, as did black patients. These results matched CDC findings comparing relative diabetes incidence among different age groups and races,[10,11] and simulations based on the CDC results reached similar conclusions to those based on the NHANES data. While incidence rates for specific 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.[12] 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 published data has shown that these rates may be decreasing, and the death rates arrived at by the Nelder-Mead optimization were similar to those found in these sources.[13]

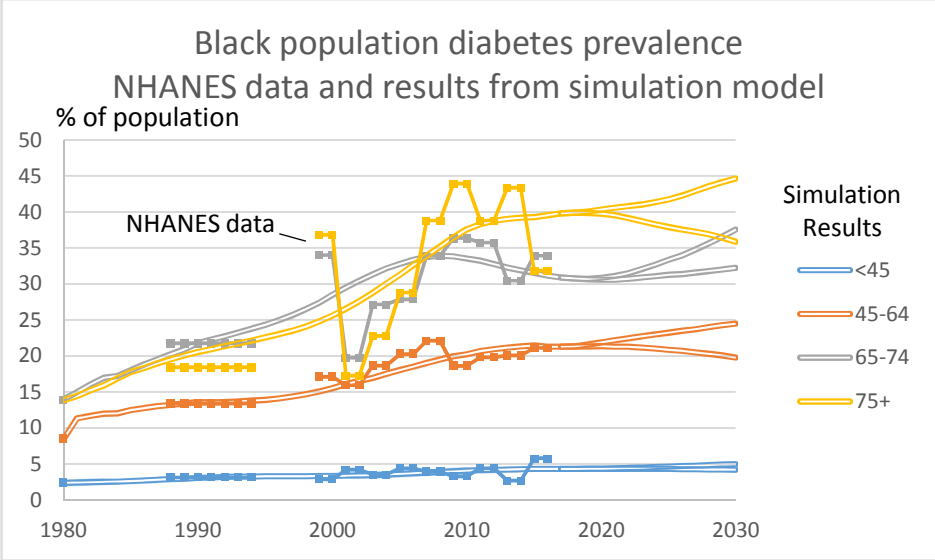
The NHANES data in Figure s2 illustrate the dilemma when attempting to use estimates based on the most specific group possible; even with the large samples available and sophisticated sampling methodology, the NHANES estimates of diabetes prevalence vary quite a bit within age/race groups from survey to survey. See Supplemental appendix 7: Smoothed population estimates for more discussion on how this was dealt with in the modeling process.

Supplemental Figure s2: Annual diabetes prevalence from 1980 to 2013 by age group, for racial groups used in simulation: (a) White, (b) Black, and (c) Other.

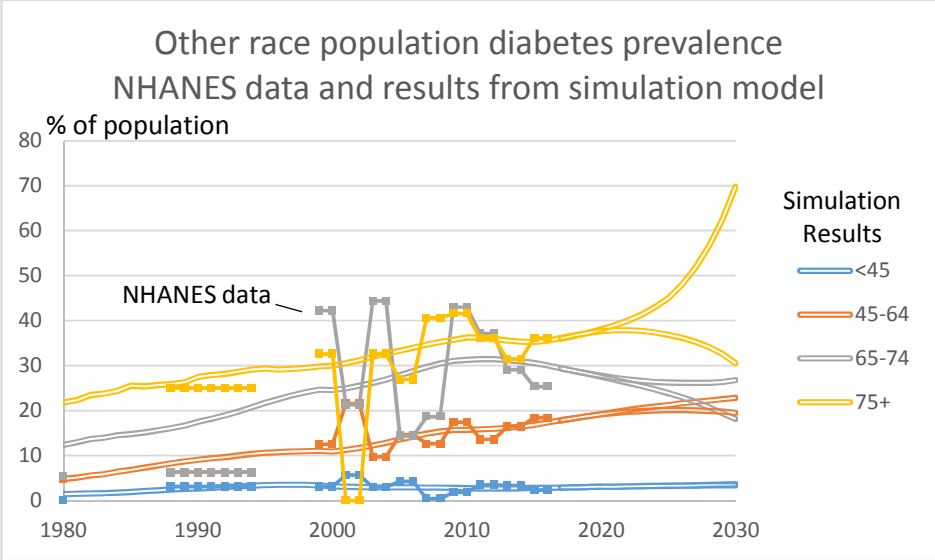
(a) White



(b) Black



(c) Other



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.[14,15] Eighty percent of the adult population with diabetes is overweight or obese.[16] We used both CDC National Health And Nutrition Examination Survey (NHANES) and National Health Interview Survey (NHIS) data on the self-aware (i.e. diagnosed) diabetic population in separate runs to describe the population at most risk of ESRD with diabetes identified as the primary cause. Both sets of runs projected similar increases in the diabetes and ESRD population.

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.[17] Projections were calculated based on simulated incidence and post-1996 death rates.

When using NHANES data, the obesity and diabetes prevalence for people over the age of 75 who were neither white nor black was 0% in the 2000-01 dataset. We used instead interpolated rates based on the adjacent NHANES datasets. Similarly, data for patients over the age of 75 were missing from the 1976-1980 NHANES data; we used values that were proportional to the 65-74 year-old values, based on proportions calculated using the 1988-2000 data.

The prevalence of diabetes per million population is expected to increase to 11-13% of the population, compared to 9% in 2016, but due to the increase in population, the prevalence count of people with diabetes is expected to increase by 46%-67% between 2015 and 2030; this range agrees reasonably well with estimates found in other literature, such as 54% in Rowley et al.[18]

Currently, fewer than 10% of U.S. patients in the early stages are aware of their kidney disease; furthermore, even among patients with a CKD diagnosis, diabetes, or hypertension, only 43%-48% had received urine albumin testing.[19] Programs that increase awareness may lead to earlier detection and, through preventive interventions, reduced ESRD incidence.

Supplemental Appendix 6: *Hypertension and other ESRD causes*

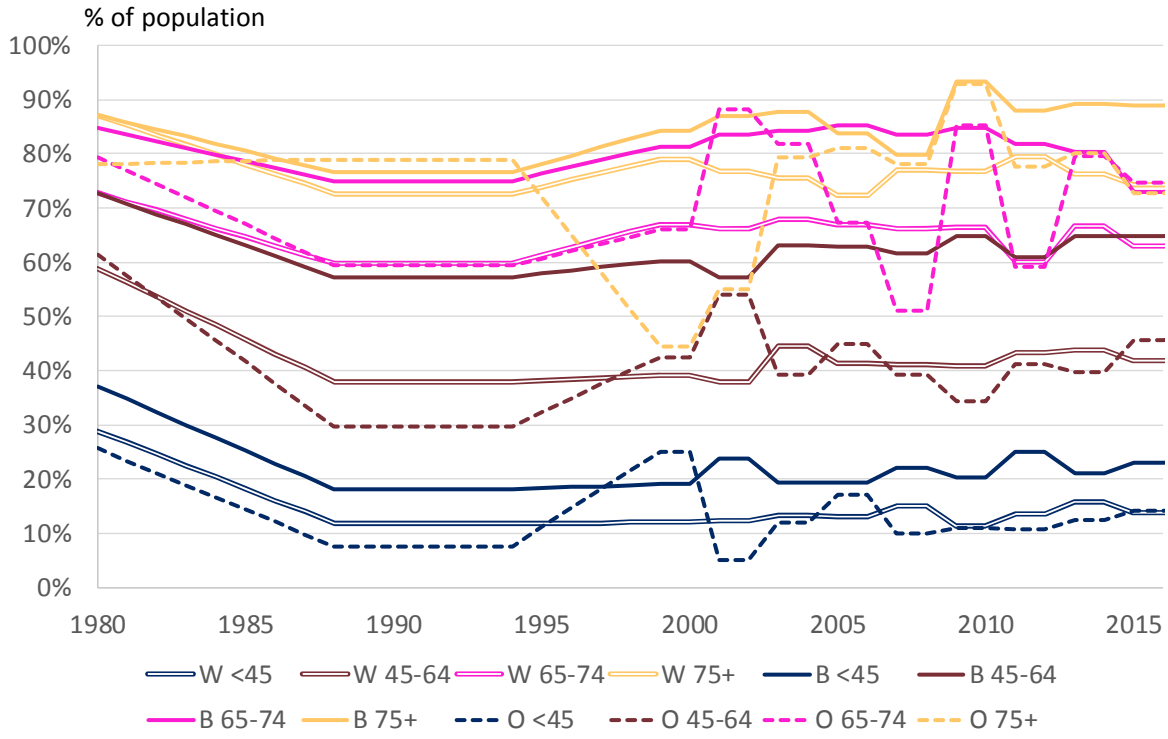
Hypertension prevalence and projections

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,[20] 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.[21] While the prevalence of hypertension differs a great deal by age and race, Figure s3 below indicates that it has not varied a great deal over time within these groups.

Supplemental figure s3: Prevalence of hypertension by year, age, and race group based on NHANES data.



As a result, we lacked observational data that indicated the population-level influence of obesity on hypertension levels, and while obesity is a recognized risk factor for individual patient hypertension, this causal factor was omitted from the simulations of population data. 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.

ESRD incidence attributed to other causes

In 2013, the USRDS attributed 73% percent of all ESRD incidence to diabetes or hypertension as the primary cause.[22] The remaining ESRD 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 ESRD were used to project trends through 2030. The R^2 values for linear regression models were 0.96 for most ESRD 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. While obesity can exacerbate or be a causal factor in some of these other conditions, this mechanism was treated as ignorable in these simulations.

Supplemental figure s4: ***ESRD prevalence proportion (per million) by assumptions of obesity and ESRD death-rate trends after 2015 (a-d), age/race group (color coded), and year (observed [dashed curves] and simulated through 2015; projected after 2015 [solid curves])***

The figures provided in the report show ESRD prevalence by age and separately by race in order to simplify the display. The following figures show ESRD prevalence by race and, within each race category, by age group as well.

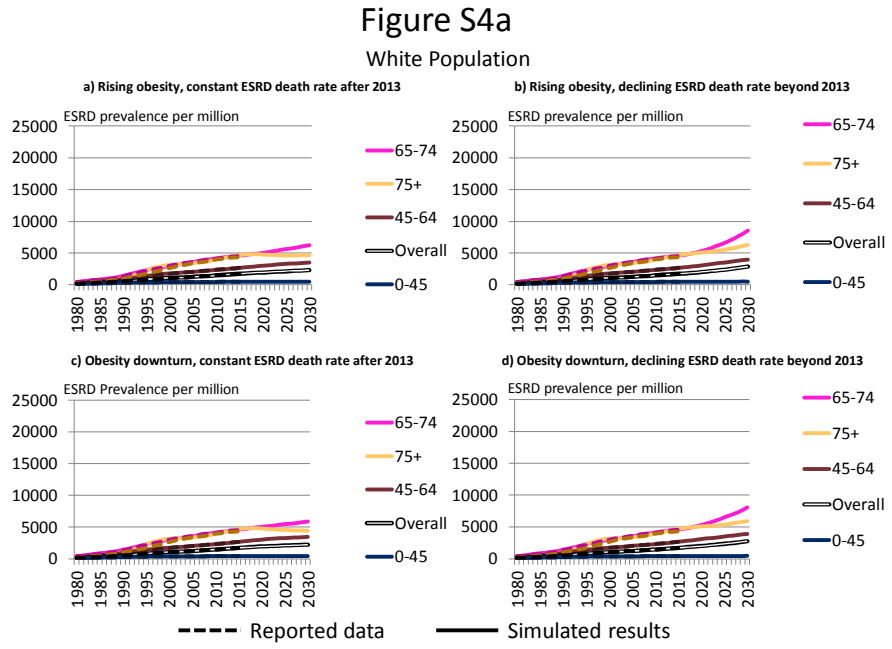


Figure S4b

Black Population

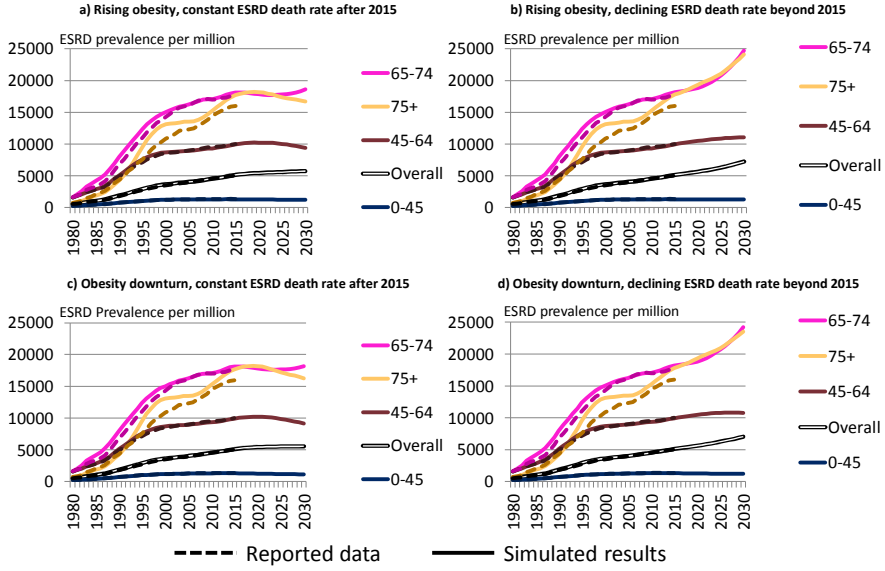
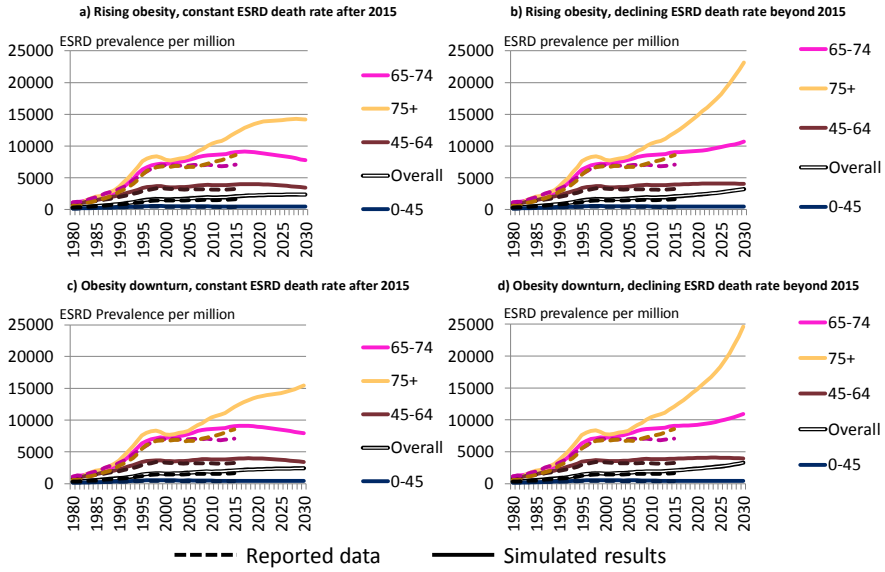


Figure S4c

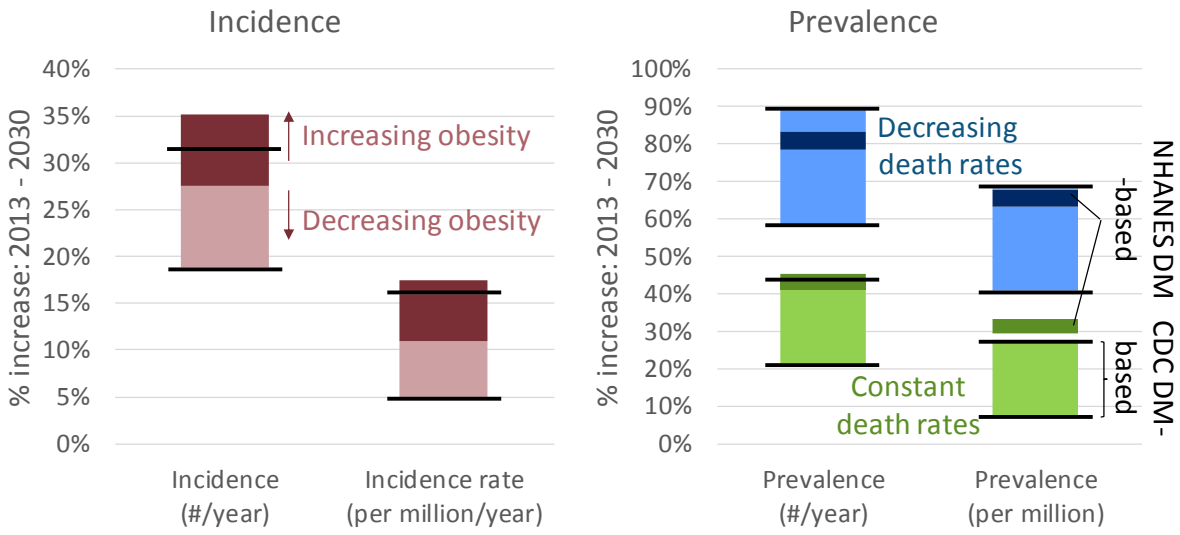
Other Race Population



Supplemental appendix 7: ***Sensitivity to racial categories, source of diabetes information***

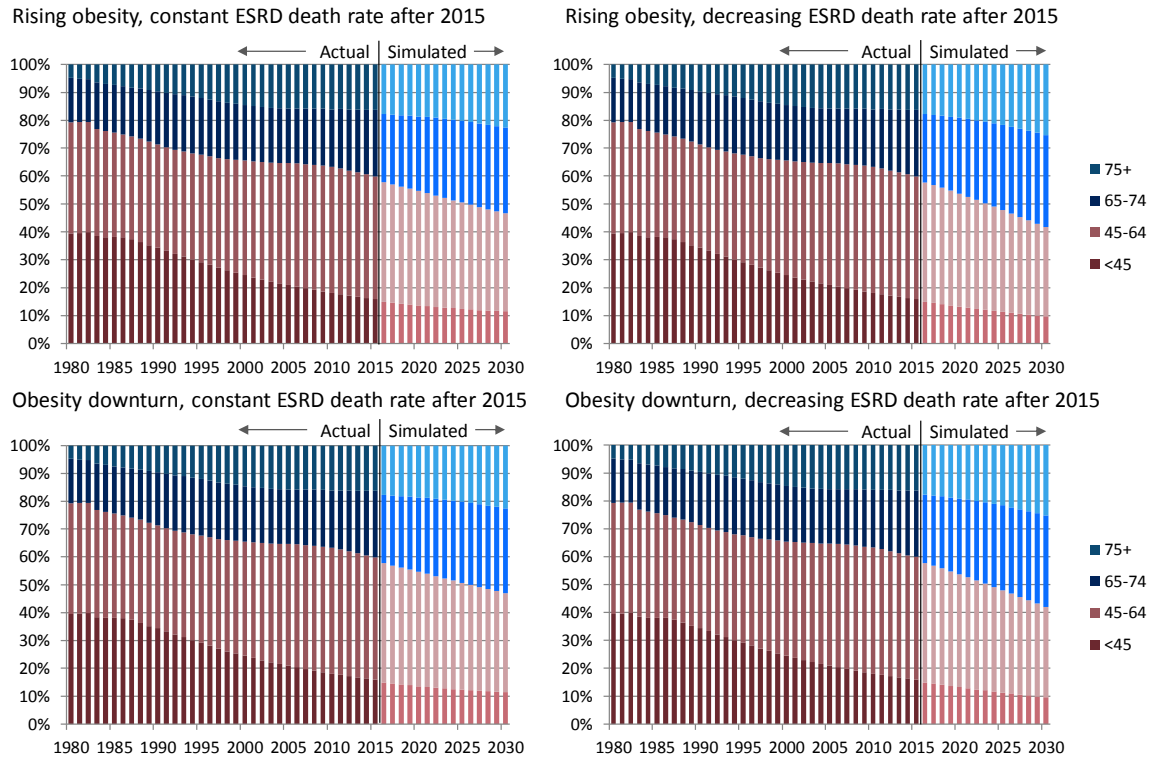
We ran the simulations using data from the CDC on age- and race-specific diabetes prevalence. This is based on self-reported diabetes, which has the disadvantage of not capturing undiagnosed diabetes and generally reports lower prevalence than diabetes based on NHANES data, which is what was presented in the manuscript. Using this data, we ran alternative models using either three racial groups (black, white, other) versus two (white, non-white). Figure s7 shows the range of projected increases in ESRD incidence and prevalence using these alternative data sources, compared with the projections used in the manuscript. In every run, there was substantial growth in the ESRD population. The runs based on CDC National Health Interview Survey diabetes prevalence and two racial groupings tended to have the lowest growth, followed by the runs using CDC diabetes prevalence and three racial groupings. The runs based on NHANES data using three racial groupings tended to have higher estimates; the fact that they were also based on more recent data (through 2015 instead of through 2013 for the runs based on CDC diabetes data) may have also contributed to this and to the narrower band of results. The three-race simulations generally exhibited more instability, especially when estimating trends in the smaller groups (e.g., 75+, other racial group). The larger estimates may represent improved accuracy due to including more specific patient categories in the simulation models; alternatively, they may reflect more unstable estimates due to smaller cell sizes. We believe that the three-racial group models using NHANES data provide the most accurate projections, and have focused the manuscript's results on these runs.

Supplemental figure s5: ESRD projections based on different data sources and race groups



Legend: Darker colors within each bar indicate range of estimates using NHANES diabetes data and three racial groups (black, white, other). Dark bars indicate range of estimates using CDC diabetes prevalence and either two (white, non-white) or three racial groups.

Supplemental Figure s6: Age distribution of prevalent ESRD patients, by obesity assumption and death rate assumption



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