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DISSERTATION

Preserving Health among Vulnerable Populations

Three Essays

Xiaohui Zhuo

This document was submitted as a dissertation in June 2009 in partial fulfillment of the requirements of the doctoral degree in public policy analysis at the Pardee RAND Graduate School. The faculty committee that supervised and approved the dissertation consisted of Emmett Keeler (Chair), Susann Rohwedder, Roberto Vargas, and Shinyi Wu.

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Published 2009 by the RAND Corporation
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Dissertation Abstract

This dissertation consists of three stand-alone essays that focus on the economics of preserving health among vulnerable population, specifically chronic ill and elderly population.

First paper focuses on elderly population. It examines Medicare Part D beneficiaries' choice of when to take up Part D in its initial enrollment period (IEP). The findings show consumers responded to financial incentive embedded in Part D and made their decision accordingly. Elderly consumers tend to enroll earlier if they were facing higher level or greater variation of prescription drug out-of-pocket spending. The result also implies the need of public effort to facilitate the enrollment decision.

Chronic Kidney Disease (CKD) is increasingly a public health concern in the United States. In the second paper, we developed a microsimulation model as a base of cost-effectiveness analysis of alternative CKD intervention strategies. Using a nationally representative sample, the model generates a large number of life histories over the next 20 years. The model provides a consistent analytical framework for the evaluation of alternative CKD interventions.

The third paper examines the impact of improving high blood pressure control on CKD outcomes at population level. The strategy was found improves the health outcomes of CKD and save life-time medical cost. The cost savings on the ESRD associated health care is substantial, offsetting the investment on the upstream hypertension control. The results support that more public health efforts should be directed to improve the hypertension awareness and control as one effective early intervention strategy on CKD.

Acknowledgements

I would like to acknowledge the many people who provided support and guidance during this study. I am grateful to my dissertation committee members, Emmet Keeler, Shinyi Wu, Roberto Vargas and Susann Rohwedder for their instructive contribution to my research as well as to my professional training. My committee has given me tremendous support and understanding during my sickness while writing the thesis. Through all my time at PRGS, Emmett has mentored me with great patience and enthusiasm. I would also like to thank him leading me into the field of health economics. Shinyi has always had great confidence in me and my work, and provided me support without reservation. Roberto has inspired this research from a very early stage and his patience, guidance and desire for me to learn and conduct evidence-base decision analysis were essential to the completion of my dissertation. Susann, as the first RAND researcher I worked with, opened the gate of real policy research for me. What I learned from Susann will be a life-time treasure for my academic career. I would like to extend a special thanks to my external reviewer, Dr. Rob Boer, for taking time from a very busy schedule to provide responsive and substantive comments.

This dissertation would not have been possible without the generous sponsorship by Kip and Mary Ann Hagopian, and the financial support from the Charles Drew University/RAND/UCLA Comprehensive Center for Health Disparities in Chronic Kidney Disease (U54 RR019234 NCRR/NIH) and RAND Roybal Center for Health Policy Simulation.

Finally, I want to thank PRGS faculty, staff and students for their support and help during my dissertation work.

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Chapter 1 Signing up for Medicare Part D: What Were the Main Determinants for Enrollment Time?

Abstract

Medicare Part D legislation mandated a market in which private insurance companies would compete to offer coverage and consumers would have a choice of carriers and plans. A cornerstone of a well functioning competitive market is rational choices by consumers. This paper examines beneficiaries' choices regarding when to sign up for Part D during the Initial Enrollment Period (IEP). Using the most recent U.S. Health and Retirement Study data, the paper provides empirical evidence of consumers' rationality in the Part D market. The findings show that consumers responded to financial incentives related to the timing of enrollment embedded in Part D and made their decisions accordingly. Elderly consumers tended to enroll earlier if they were facing a higher level or greater variation of prescription drug out-of-pocket expenses prior to the implementation of Part D. Forty-five percent of Part D active enrollees experienced difficulties choosing a plan and were more likely to delay enrollment, suggesting that transaction costs in the Part D program are important. Furthermore, seniors who had no prior coverage for prescription drugs tended to enroll later, at least in part because they were more likely to experience difficulties choosing a plan.

Introduction

The Medicare prescription drug program (Part D) was enacted in 2006—the greatest expansion of Medicare since its inception in 1965. The Part D legislation mandated a market in which private insurance companies and HMOs would compete to offer coverage, and consumers would have a choice of providers and plans. In order to enroll in Part D, consumers have a series of decisions to make, including whether to sign up, when to sign up, and which plan to choose. The cornerstone of making the competitive market work is the assumption that a critical mass of consumers will make rational choices. However, the complicated design of Part D raised concerns about whether seniors would be able to make rational choices consistent with their self-interest.

This paper examines one aspect of consumers' rationality by studying their choice of *when* to sign up for Part D during the initial enrollment period in 2006. There are two concerns with respect to consumers' decisions about the timing of enrollment. First, elderly consumers may not have the attention and acuity needed to navigate through the complicated system and make a rational decision. As a result, they may enroll late, which may subject them to the risk of increased spending on medication and the late-enrollment penalty. Second, for many healthy consumers, the costs of enrolling are borne immediately, but the benefits only come in the future when prescription drugs are needed. Consequently, consumers with time-inconsistent preferences might not be able to recognize their future need and may postpone enrollment. The purpose of the analysis in

this paper is to understand how well elderly consumers responded to the economic incentives embedded in Part D that pertain to the timing of the decision to enroll.

The primary finding is that Medicare beneficiaries did respond to these financial incentives, timing their enrollment in Part D in a way that aligned with their own interest. However, those who experienced difficulties tended to delay their sign-up. Consumers tended to enroll earlier if they previously faced a higher level, or greater variation, of out-of-pocket spending on prescription drugs. Consumers in better health were more likely to enroll later, consistent with the expectation that the immediate benefit of enrollment would be smaller for them. Forty-five percent of enrollees experienced difficulties choosing a plan. This group tended to delay their uptake, suggesting the important role of transaction costs in enrollment in Part D. Furthermore, those elderly who had no prior prescription medication coverage tended to enroll later, at least in part because they were more likely to experience difficulties in choosing a plan.

Background

The fastest rising of all health care costs, expenditures on prescription drugs increased 17.3% overall from 1999 to 2000 in the United States. In 2002, spending on prescription drugs accounted for 15.3% of total national health expenditures (Heffler, et al., 2004). As new and expensive drugs have come into use, patients—particularly more vulnerable senior patients—have found prescription drugs more difficult to afford. After nearly six years of debate in Congress, a federal program to subsidize the cost of prescription drugs for Medicare beneficiaries, the so-called "Medicare Part D," was introduced to protect

seniors from the high cost of drugs. The program was enacted as part of the Medicare Prescription Drug Improvement and Modernization Act of 2003 (MMA) and took effect on January 1, 2006.

The assumption that consumers – or at least a critical mass of consumers – will make rational choices is the cornerstone of the success of the consumer-directed healthcare program. Part D is "a massive social experiment on the ability of a privatized market to deliver social services effectively."[1] Private plans compete to bid for providing benefits and receive payment both from government contributions and enrollee premiums. The government shares the risk with the private drug plan providers through reinsurance (80% of allowable drug costs exceeding the stop-loss threshold) and risk corridors. The intention underlying the Medicare Part D design is that private competition and the free market will keep costs down, offer more choices, and allow each participant to tailor his or her Part D insurance to meet his or her particular needs. In the mandated market, consumers are given the right and responsibility to make enrollment choices. If consumers can rationally make choices aligned with their self-interest, the competition among private plans will ensure a match between demand and supply, achieving cost-efficiency. But if a large group of consumers is confused, the market will not get the signal to function efficiently.

In view of the complex design of the Medicare Part D program, there is reason to doubt that seniors are able to make rational choices about enrollment in the program. To enroll,

[1] McFadden, D. "A Dog's Breakfast", Commentary, Wall Street Journal, Feb 16, 2007. http://online.wsj.com/article/SB117159975453110920.html, accessed on Oct, 2008.

consumers have to make a series of decisions within a limited enrollment period. The nature of the decisions varied as a function of individual's prescription drug coverage prior to Medicare Part D. We distinguished four scenarios:

1. The first scenario involves people eligible for both Medicaid and Medicare—the so-called "dual eligible." They could either sign up for a plan themselves before January 1st 2006, or, if they had not done so by this date, they would be automatically enrolled to ensure continuous coverage. In that case, they were randomly assigned to a plan, but could switch to another plan of their choice any time during the open enrollment period.

2. The second scenario involves people with a Medicare HMO plan. For the most part, they had no decision to make because Medicare Advantage plans were essentially required to offer drug coverage under Part D.

3. The third scenario involves consumers with other "creditable coverage."[2] These are mostly people with employer-sponsored coverage, who were encouraged to keep it.

4. The fourth scenario involves individuals with privately purchased coverage for prescription drugs and individuals without drug coverage. This group was estimated to make up nearly 40% of the total Medicare population (Neuman, et al., 2007). Individuals in this group had to decide whether to enroll in Part D, when to enroll, and which plan would best fit their needs. Our analysis will focus on this group. In most states, they had to select from a large number of competing plans with different features, such as varying drug tiers, formularies, and cost-sharing and coverage gap policies. Once a person in this

[2] Coverage is creditable if the actuarial value of the coverage equals or exceeds the actuarial value of standard prescription drug coverage under Medicare Part D, as demonstrated through the use of generally accepted actuarial principles and in accordance with CMS actuarial guidelines. Federal Employee Health Benefits Program (FEHBP), TRICARE (health benefits for the military), and Veterans Benefits are all creditable coverage. Standard Medigap policies with prescription drug coverage are not creditable.

group committed to a plan, in most cases, he or she could not change it until the next annual enrollment period. The government encouraged private companies to participate, with the result that in some states there were more than 50 plans to choose from, while nowhere was there a simple metric that people could use to determine which plan would be best for them.

In addition to deciding on a particular plan, consumers in the fourth scenario also had to decide *when* to sign up. At the inception of Part D, consumers could sign up within a seven-month initial enrollment period, which began on November 15, 2005 and ended on May 15, 2006. They could also choose to wait until a need for medication arose. If an individual without creditable coverage decided to enroll after the initial enrollment period, s/he would bear a penalty of 1% of the monthly premium for every month that had elapsed since the end of their initial enrollment period and the time they signed up[3]. Within the initial enrollment period, consumers could choose to sign up immediately in November or December 2005, or delay until May 2006. Benefits began in January 2006 if consumers enrolled by December 2005, or in the month after enrollment, if they enrolled in 2006.

This study focuses on consumers' decisions about when to enroll during the seven-month initial enrollment period. Although the highly subsidized insurance will generally relieve the cost burden of those over the age of 65, signing up early is not necessarily optimal for all Medicare beneficiaries. The immediate premium (on average $32 per month in 2006),

[3] See Medicare Payment Advisory Commission, "Part D Plan Offerings," chap. 7 in Report to the Congress: Increasing the Value of Medicare, June 2006, http://www.medpac.gov/publications/congressional_reports/Jun06_EntireReport.pdf (accessed in May 2009)

100% cost-sharing in the "donut hole," and the complex enrollment process all may deter or delay the consumer's uptake. A rational consumer should carefully schedule his or her enrollment to maximize his or her benefit from Part D. Studying how consumers timed their uptake provides insights into whether they responded rationally to the financial incentives embedded in Part D. It also helps to better understand non-pecuniary factors that may have influenced consumers' sign up decision.

Literature

Several studies of consumer behavior emerged following the implementation of Medicare Part D in 2006. Some of these investigated the impact of Part D on changes in prescription drug utilization, adherence, medical expenditures, and how these changes relate to health outcomes. Other studies have focused on the consumer's knowledge of the program and how this relates to the enrollment decision. In this paper, we briefly review the first group of studies, but emphasize the latter because it is more closely related to our study.

Due to lack of data, there have been few studies on the impact of Medicare Part D on the utilization of medications and cost responses. Two recent studies found that the program's prescription benefit resulted in modest increases in average drug utilization and decreases in average out-of-pocket expenditures (Lichtenberg and Sun, 2007; Yin, et al., 2008). But another study by Zhang and his colleagues (2008) showed that the net impact of Part D among these beneficiaries was a modest decrease in the use of generic

drugs. Using prescription records from Wolters Kluwer Health, Ketcham and Simon (2008) estimated the reduction of out-of-pocket costs for prescription drugs to be 21.7%. They estimated the increase in prescription use to be about 5%. Duggan and Scott-Morton's study (2007) also indicates that Part D substantially lowered the average price and increased the total utilization of prescription drugs by Medicare recipients. One study found a small, but significant reduction in cost-related nonadherence (CRN) to medication following the implementation of Part D (Madden, et al., 2008). These results are based on data from 2006, the year Part D was introduced, when many beneficiaries were only covered for part of the year. A reliable assessment of the full effect will have to await analyses based on subsequent years of data.

With more empirical data now available, there is a growing number of studies on consumers' actual enrollment behavior within the initial enrollment period. Conducting telephone interviews of a sample of Medicare Advantage beneficiaries, Hsu et al. (2008) found that elderly beneficiaries have limited knowledge of Part D cost sharing and often report behavioral responses to drug costs. Limited knowledge is associated with fewer reports of cost responses overall, but more reports of financial burden. Neuman et al (2007) conducted a nationwide survey of 16,072 noninstitutionalized Medicare beneficiaries age sixty-five and older in 2006. They specifically looked into consumers' signup decisions, finding that seniors who did not sign up for Part D (and had no other coverage) generally were either potentially hard to reach or in relatively good health. Furthermore, they found that Part D enrollees had higher rates of out-of-pocket spending

and greater cost-related nonadherence than seniors covered through employer plans or the Veterans Administration.

Hurd et al (2007) conducted a hypothetical plan choice experiment in the American Life Panel, an Internet panel maintained by The RAND Corporation's Labor and Population Division. They found a weak relation between the preferences of consumers and the cost ranking of prescription drug plans. The explanation they suggest is that consumers are not fully informed about their drug costs. Levy and Weir's (2007) results from the Health and Retirement Study (HRS) suggest that uptake of Part D was driven primarily by economic considerations: In particular, those who used more prescription drugs or had worse self-reported health in 2004 were more likely to sign up for Part D. The reasons that respondents stated for declining Part D suggest that people were confident about their decisions and that confusion was not a significant factor keeping potential beneficiaries out of the program. But Levy and Weir (2007) did not investigate how consumers decided when to sign up for Part D. The study does not make it clear whether confusion might be a factor keeping beneficiaries from making rational timing or planning decisions.

Recent studies by Heiss, McFadden and Winter systematically investigated the rationality of consumers' enrollment choices regarding the Part D program. Using the Retirement Perspective Survey (RPS) conducted before and after the deadline for enrollment in Part D, Heiss et al studied the role of prescription drug use and health risks, related expectations, and subjective factors in the demand for prescription drug insurance. They

estimated that about 24.4% of the population age sixty five and older is healthy enough that it might have been rational to delay enrollment at the monthly premium of $37 originally projected by the CMS (Winter, et al., 2006). In particular, Heiss et al. (2007) studied actual enrollment decisions made in the initial enrollment period, including whether or not to enroll in Part D, the timing of enrollment, and the choice of plans. Their findings show that "seniors respond to the incentives provided by their own health status and the market environment as predicted by the optimization model." However, seniors seem "short-sighted and over-reacted to 2006 prescription drug costs, while being little sensitive to future costs."

Studying 349 Part D enrollees, Heiss et al (2007) found that drug costs in the year before enrollment appear to have a strong impact on the choice of signup time—especially on early enrollment by December 2005 and additional enrollment by March 2006. However, it predicts late enrollment weakly. The paper concludes that the rational decision whether or not to enroll early mainly depends on whether the individual expects immediate benefits in 2006. The decision to enroll early depends primarily on expected drug costs in 2006. Late enrollment within the initial enrollment period is rational for individuals who do not expect immediate benefits in 2006, but want to avoid the late enrollment penalty.

While the study by Heiss et al (2007) provides important insights, two limitations need to be pointed out. First, their analysis does not take into account other non-pecuniary barriers to participation. Evidence from other surveys suggests that more than 60% of Medicare beneficiaries reported difficulties in understanding the Medicare Part D

program and choosing a plan (Hsu, et al., 2008; Hurd, et al., 2007). To sign up for Part D in an informed manner, consumers had to spend substantial time and mental effort to inform themselves about the various options available and make a decision. The related transaction costs might significantly reduce the value of the program and discourage consumers from enrolling in Part D early. It is important to understand whether consumers delayed uptake because they are "irrational" or due to the high transaction costs, because the two hypotheses have different policy implications. Second, the generalizability of their results may be limited due to the relatively small sample size (N = 349).

Conceptual Framework

In this paper, we focus on the decision of when to enroll in Part D. We analyze financial aspects of this decision as a consumers' cost minimization problem. Although we do not estimate individuals' transaction costs, we investigate whether consumers reported difficulties when they were making a decision. We use data from the Health and Retirement Study (HRS) to estimate the effect of out-of-pocket costs and the presence of difficulties. An important advantage of using data from the HRS is its longitudinal nature with rich retrospective information about individuals' coverage status and out-of-pocket costs. It allows us to examine the uncertainty of consumers' spending on prescription drugs, their coverage status prior to Part D, and how these two things relate to the timing of enrollment. The second advantage of HRS is the much larger sample size and rich and high-quality covariates available in the data. In 2006, more than 10,000 Medicare beneficiaries were interviewed during the Part D IEP period. 2,974 of those who

responded actively enrolled in Part D. Additionally, there is a wide array of individual and household variables available in the HRS, including high quality income and wealth variables.

Let TC denote the total annual prescription drug cost that we assume to have occurred uniformly over the year 2006. To simplify the problem, we assume that consumers did not change their utilization of prescription drugs because of signing up for Medicare Part D. The decision variable t is constrained from 0 to 5, where 0 stands for enrollment on November or December 2005 and 5 stands for the last month of penalty-free IEP. Benefits were effective in the month following enrollment if consumers signed up in 2006, or January 2006, if they signed up by 2005. Let OOP_1 and OOP_2 denote the out-of-pocket prescription drug spending before and after enrollment in Part D respectively. The objective function can be written as:

$$\begin{aligned}
&\underset{t}{Max}\left[E\left(NetBenefit\right)\right] = \underset{t}{Min}\left[E\left(ConsumerCost\right)\right] \\
&= \underset{t}{Min}\left[\delta_1 E\left(OOP_1(t)\right) + \delta_2 E\left(OOP_2(12-t)\right) + \delta_2(12-t)P\right] \\
&= \underset{t}{Min}\left\{\delta_1 \frac{t}{12} E\left(TC\right) + \delta_2 f\left[\left(1-\frac{t}{12}\right) * E\left(TC\right)\right] + \delta_2(12-t)P\right\}
\end{aligned}$$

where $f\left[\left(1-\frac{t}{12}\right) * E(TC)\right]$ implies the out-of-pocket spending after enrollment. It is a function of the total prescription drug cost and enrollment time. P is the monthly premium. δ_1 is the discount factor for pre-Part D months, and δ_2 is the factor for post-

Part D months.[4] The discounting is needed because of consumers' time preference: Future cost is weighted less than present cost ($\delta_1 > \delta_2$). The formula of out-of-pocket spending in 2006 after enrollment in Part D is:

$$\begin{aligned} OOP_2 &= f(C) \\ &= Min(C,250) + .25 * Min[2000, Max(0, C-250)] \\ &+ Min[2850, Max(0, C-2250)] + 0.05 * Max(0, C-5100) \end{aligned}$$

where $C = E(TC) * \left(1 - \frac{t}{12}\right)$. As shown in Figure 1, consumers' out-of-pocket spending is a function of the total drug cost in 2006[5]. The net benefit is calculated as the cost saving from enrollment in Part D (i.e. $TC - OOP_1 - OOP_2 - 12 * P$). Both consumer costs (including out-of-pocket costs and premium) and the net benefit (cost savings on prescription drugs due to Part D) are shown in Figure 1 for the scenario where the consumer signs up at the beginning of 2006. Consumer costs increase with total medication costs. For some low medication users, their total consumer costs would be higher than their actual medication costs because of their premium. For example, consumers with annual total prescription drug costs of $250 would have to pay $634 in total ($384 as the premium and $250 out-of-pocket as the deductible). If the total annual cost for prescription drugs falls within the range of $2250 to $5100—the so-called "donut hole"—the line of total medication costs would parallel the line of the total consumer costs, because consumers have to pay 100% of their prescription drug costs. Once it

[4] Restrictively the discount should be calculated month by month. However, for simplicity we calculate them as only two periods: pre-Part D and post-Part D in 2006.

[5] Here we assume the consumers signed up in November or December 2005, so were covered for the full year of 2006

becomes more than $5100, the net benefit almost parallels the total medication costs because Part D would cover 95% of the prescription drug costs.

In the simple model, we assume that a rational consumer is aware of his or her total expected prescription costs in the coming year and makes a decision based only on the financial outcome. Individuals would sign up for Part D at the time when they expect the lowest total consumer costs, or largest net benefit. For consumers with a low annual pharmacy bill, it may not be desirable to sign up early. However, consumers whose demand for prescription drugs is high will maximize the net benefit by immediately enrolling. Figure 2 exhibits the total consumer costs under three enrollment scenarios: enroll early (before 2006), enroll in the middle (March 2006), and enroll at the end (May 2006). As shown in the figure, consumers' costs increase with the total drug costs and consequently, the optimal enrollment time varies. Specifically, (1) if total drug costs are lower than $550, the consumer's cost is lowest if he or she chooses to enroll in May 2006; (2) if the total drug costs fall between $550 and $3,000, signing up early is the dominant strategy (for example, a consumer with total annual drug costs of $2,250 will save $543 if she chooses to sign up by 2005 versus in May 2006); (3) for consumers with a total pharmacy bill roughly ranging from $3000 to $5100, the difference between signing up early or late becomes ambiguous; (4) if consumers are heavy spenders with annual medication costs of more than $6,000, they will save more by enrolling earlier. Signing up for Part D by 2005 would save them at least $2,066, compared with a savings of $1,276 if they were to wait until May 2006.

Considering the transaction costs to consumers of signing up for the program, we make a small modification to the model. Considerable evidence has suggested that transaction costs are important determinants of the uptake of social programs (Currie, 2004). In the case of Part D enrollment, transaction costs could include any pecuniary or non-pecuniary cost that consumers had to incur to learn about, and apply for, the social program. Therefore, we modified the consumer's objective function by adding a one-time transaction cost, shown as follows, where C denotes the transaction costs:

$$Min_t\left[E\left(ConsumerCost\right)\right]$$
$$= Min_t\left\{\delta_1 \frac{t}{12} E\left(TC\right) + \delta_1 C + \delta_2 f\left[\left(1-\frac{t}{12}\right) * E\left(TC\right)\right] + \delta_2 (12-t)P\right\}$$

As shown in Figure 3, adding transaction costs leads to an upward shift in the consumer's total cost. Because the one-time transaction cost is valued more at present, early enrollees will face a greater increase in total consumer costs with additional transaction costs. When the increase is sufficiently large, it might change a consumer's optimal signup time. This is demonstrated in Figure 3. For consumers with total drug costs of around $700, it is clearly better to enroll earlier if there are no transaction costs. However, with additional transaction costs, the early enrollment line shifts up so that it lies above the late enrollment cost line, indicating that it is more advantageous to postpone enrollment. This is consistent with our intuition that an individual tends to postpone the decision to enroll if the decision-making process itself is costly.

In sum, pecuniary costs and non-pecuniary barriers can both play roles in a consumer's decision. The simple economic model illustrates how they influence a rational consumer's decision with respect to the timing of signup. Next, we will present empirical evidence from the Health and Retirement Study.

Study Data and Methods

The data we used is from the U.S. Health and Retirement Study (HRS), a nationwide survey of the U.S. population age 51 and over. The baseline survey was conducted in 1992 and follow-ups were done biennially. In addition to demographics and major economic outcomes (including participation in the labor force, income, wealth, and pensions), the HRS collected detailed information about respondents' health and health insurance. Since 1995 (Aging & Health Dynamics, or AHEAD), the HRS has increasingly collected information about respondents' prescription drug insurance, including whether they had coverage, the coverage sources, premium, and their out-of-pocket spending. In the 2006 survey, conducted between March 2006 and February 2007, the HRS additionally asks about participants' enrollment status in Medicare Part D:

Beginning in 2006, Part D of Medicare provides coverage for prescription drugs. Have you signed up for the new Medicare prescription drug coverage?

If respondents reported having signed up, but were not automatically enrolled or assigned a plan, they were subsequently asked about the time they had signed up. The specific question is:

About when did you sign up (for the new Medicare prescription drug coverage)? Month? Year?

Of 10,393 Medicare non-dual-eligible beneficiaries interviewed in 2006, 2,974 reported that they had actively signed up for Part D and chosen plans by themselves. This group was consequently asked the question about enrollment time. It forms the basis of our analytic sample. There are, however, two potential concerns. The first is right censoring. There is an overlap between the HRS 2006 interview window (from March 2006 to February 2007) and the initial enrollment period of Medicare Part D (from November 2005 to May 2006). Therefore, some enrollments cannot be observed in the interviews. Specifically, if respondents were interviewed before May 2006, but decided to sign up after that May, their enrollment would not be observed in our data. Of these non-enrollees who were interviewed before May 2006 (N = 1,680), 117 reported that they had not decided whether to enroll or not at the time of the interview. We suspected that they were likely enrolled after the interview. As a sensitivity test, we added them to the original analytic sample in the regression analysis.

The second issue is missing information on the timing of enrollment, the outcome variable in our analysis. The information is self-reported, so the data quality is, to some

extent, subject to respondents' recollections. Of 2,974 active deciders, 274 reported their enrollment time beyond the IEP range or missing. Fifty-three of them were found to have had creditable coverage before they enrolled. We excluded these 53 respondents from the sample because they were not subject to the penalty for late enrollment. Among the remaining 2,921 respondents, 221 (8%) were missing the enrollment time. This left us with a final sample of 2,700 respondents. Losing part of the sample due to missing information raises the concern that the remaining sample might not be representative of the study population, and that the selection is not random in terms of the relationship between explanatory variables and enrollment time. We therefore compared the basic characteristics between the "missing" and "non-missing" samples (see Table 1). We found that the "missing sample" is less educated; has more minorities; and is single, poorer, and in worse health, which suggests a need to adjust the sample selection.

To investigate the determinants of the timing of enrollment for Medicare Part D we estimated an ordered probit model with enrollment time as the left-hand variable, distinguishing three outcomes: "early enrolled" (November and December 2005), "intermediate enrolled" (January to March 2006), and "late enrolled" (April and May 2006).[6] The propensity to sign up later rather than earlier was modeled as a linear function of the individual's out-of-pocket cost prior to Part D in 2006, whether the

[6] Enrollment time is recorded in the survey by single month from November 2006 through May 2007, allowing for a more detailed categorization of the left-hand variable. We estimated the ordered probit model with both versions of categorizing enrollment time, the one distinguishing single months of sign-up and the one distinguishing between early, intermediate and late enrollment. We only present the results based on the version with just three categories for several reasons: First, the results show no significant difference. Second, the benefit was effective starting from January 2006 for consumers who enrolled in November and December 2005, making it natural to combine them as one group. And third, we included 117 respondents in the regressions who were "suspected" enrolled after March 2006. While the information of the exact month of enrollment is missing, these observations fit into the category "late enrolled".

individual experienced difficulties choosing a plan, health conditions and other individual characteristics. The relationship to be estimated can be written as:

$$y_i^* = \beta_1 \ln(OOP)_i + \beta_2 Diff_i + \delta X_i + \varepsilon_i$$

where y_i^* is the individual's propensity to sign up late, $\ln(OOP)$ is the natural logarithm of the individual's monthly out-of-pocket cost prior to Part D, and $Diff_i$ is an indicator variable for whether the individual experienced difficulties in choosing a plan. β_1 and β_2 are the parameters associated with the two key explanatory variables. The vector X_i contains a set of other individual characteristics. ε_i is an error term that is assumed to have a standard normal distribution.

We used respondent reports on OOP cost elicited right before enrollment as a proxy of consumers' expected total prescription drug cost in 2006. Two respondents reported monthly OOP over $10,000. After checking that these individuals did not have any severe medical conditions we assumed that these two reports were due to some form of measurement error and set them to missing.[7] Additionally, if respondents did not regularly take medications or reported that their prescription drug costs were completely covered by insurance, they would be skipped out of the OOP spending question. In both cases, we assigned zero to OOP costs. Their log forms of OOP values, as well as the ones of other respondents reporting zero OOP cost, were assigned the value zero.

[7] The outliers are so large that they affect the regression results.

Individuals who face considerable uncertainty about their prescription drug needs due to having experienced large variation in OOP on prescription drugs in the past may be inclined to sign up earlier to take advantage of the insurance value of Part D. Even though we did not include this aspect in our theoretical framework, we do investigate this possibility in our empirical analysis and include the within-individual standard deviation of monthly OOP costs over last 10 years as a proxy for individuals' uncertainty about prescription drug spending.

Other covariates included in the model are whether the individual's prescription drug costs were covered by insurance before Part D, self-rated health, whether total household income is less than $30,000, age at the time of Part D enrollment, gender, race/ethnicity, and education level. Missing values in any of these variables (about 3-4%) were replaced with zeros and corresponding missing flags were included in the regressions.

In our empirical analysis we also investigate the importance of the right-censoring problem, that is the fact that for respondents interviewed before the end of the IEP who had not signed up for Part D at that time, we do not know whether they still did sign up until May 2006. To that end we ran the same regression analyses on three different samples: (1) sample 1: among the final sample (N = 2,700), we selected only the respondents who were interviewed after May 2006 (N = 1,903). (2) sample 2: the final sample (N=2,700). According to the design of the HRS interview schedule, subjects' interview times were randomly selected so that there should be no systematic difference between sample 1 and sample 2. To verify this, we compared the two samples and found

indeed no significant differences in individual demographic characteristics, health, SES, prescription drug utilization and insurance, and other characteristics. In the absence of any systematic relation between interview time and the left-hand variable also the probit estimates of the relationship of interest from the two samples should not be significantly different. (3) Sample 3: adds 117 "suspected" active enrollees into sample 2. We assume the 117 respondents signed up Part D after the interviews and investigate whether the estimation results are sensitive to the inclusion of these additional observations.

To minimize the potential bias from losing observations due to missing values in the outcome variable, we modeled whether an individual was included in the analytic sample. We ran a logistic regression with the dependent variable of whether a respondent is included in the final sample. As regressors we included demographic variables, health and economic conditions, whether the interview was by proxy, and whether the individual had cognitive problems at the time of the 2006 interview. We predicted the probability based on the regression, and then multiplied the sample weight by the inverse of the predicted probability.

Results

Descriptive analysis

In the final sample (i.e., sample 2, N = 2,700), 62% of the respondents are female and the average age is 73.5. More than 90% were regularly taking prescription medications. 95%

of the sample had been diagnosed with at least one major medical condition,[8] and nearly 40% of enrollees rated their health as poor. The distribution of the timing of enrollment within the seven-month initial enrollment period is exhibited in Figure 4.

Consumers who regularly took prescription drugs or who had high out-of-pocket costs before Part D was implemented were more likely to sign up early (see Table 2 and Figure 5). In Figure 5, we divide the sample into three groups by enrollment time and show the cumulative distribution of monthly out-of-pocket costs by group. Table 3 shows the mean, median, and standard deviation of out-of-pocket costs right before Part D and over the last 10 years. All decline with the enrollment month. Taking the early enrollees as an example (i.e., those who signed up in 2005), their monthly out-of-pocket spending is $100 higher on average than their peers who signed up in May 2006. Moreover, both the sample standard deviation and the within-individual standard deviation[9] of out-of-pocket costs are greater among early enrollees. This suggests that consumers were aware of the uncertainty of their need for prescription drugs, and tended to buy Part D coverage earlier if they faced greater uncertainty.

Consumers without prescription drug coverage prior to the implementation of Part D appeared to delay singing up and so did individuals in better health. Also those who reported difficulties in choosing a plan tended to delay signing up for Part D (see Tables 4-6). They were more likely to have no prescription drug coverage prior to Part D and to have higher out-of-pocket spending on prescription medications before enrollment; they

[8] These are the most prevalent chronic conditions among the elderly in the United States, including hypertension, diabetes, cancer, lung disease, heart disease, stroke, psychiatric disease, and arthritis.
[9] I.e., the out-of-pocket standard deviation over the last five survey waves for each individual.

were also more likely to be female, less educated, and in worse health (Table 8). We suspect that they had less experience with prescription drug insurance plans, but a higher stake in the enrollment decision, which could have made the decision more difficult for them.

Regression analysis

Table 9 presents the selected results from the ordered probit regressions using three samples. We found no significant effect of health conditions, income level, education, and other demographic variables after controlling for the key explanatory variables. For this reason, we did not present them in the table. We conducted a Hausman specification test on the estimates from the three different samples, but did not find the estimates systematically different.

The results from unweighted and weighted regressions consistently suggest that pre-Part D out-of-pocket spending has a significant negative effect on late enrollment. The odds of signing up for Part D earlier as opposed to later are approximately 1.08 times greater for consumers with 1% higher out-of-pocket costs. Variation in spending on prescription drugs is a significant predictor of enrollment timing. The consumers with the greatest variation (the 4^{th} quartile of the out-of-pocket standard deviation) are 1.2 times more likely to sign up early than those in the lowest quartile. We interpreted the within-individual standard variation as an indicator of the uncertainty about spending on

prescription drugs. To take advantage of the insurance feature of Medicare Part D, consumers with higher risk tended to sign up earlier.

We found that individuals who experienced difficulties in choosing a plan were 1.3 times more likely to sign up late. Heiss et al (2007) found that enrollment—especially early enrollment—is driven almost entirely by the cost of drugs and "very little by other variables." However, our results suggest that "difficulties in choosing a plan" also play an important role. We interpreted this as the effect of a transaction cost. Even though consumers who had difficulties managed to sign up eventually, it still implies that a social program has a reduced value if beneficiaries experience significant enrollment costs. As shown in Figure 6, we predicted the probabilities of early and late enrollment for consumers with and without difficulties in choosing a plan, and plotted them against the percentile of individuals' monthly out-of-pocket costs. For both types of consumers, higher out-of-pocket costs are associated with earlier signup. But the presence of difficulty in choosing a plan significantly increases the likelihood of delay. This is consistent with the prediction from the previous simple economic model.

Conclusion and Discussion

It is important to understand consumers' economic decision making because this has important policy implications for a consumer-directed social program like Medicare Part D. In this paper, we investigate consumers' decisions regarding the timing of enrollment in this program. Our primary finding confirms that elderly Part D consumers were

responsive to the financial incentives embedded in the program related to the timing of the decision to sign up. Our conclusion is consistent with the findings of Heiss et al. (Heiss, et al., 2007). Furthermore, our results suggest that consumers were aware if they faced risk of high spending on prescription drugs and acted accordingly when they scheduled the enrollment.

More importantly, our findings also provide suggestive evidence that the transaction costs, measured in the analysis by the difficulties in choosing a plan, play a role in consumers' decision processes. More than 45% of Medicare Part D beneficiaries in our sample reported that they had experienced difficulty when choosing an insurance plan and that that factor had been significantly associated with their delay in enrolling. Consumers who previously had no prescription drug coverage were more likely to experience difficulties. This finding suggests the need for decision-support for current and prospective Part D consumers—especially those without previous prescription drug insurance, and the less educated and less healthy.

We conclude by mentioning the limitations of the study and the directions for future research on this topic. One limitation is the potential estimation bias due to the right-censored data. Our estimation strategy lessens this concern, but does not completely address the problem. Given that the right-censored sample is apparently more likely to sign up late, our models could underestimate the probability of late enrollment. We did not apply hazard regression to address the right-censoring because this would involve modeling the decision *whether* to sign up for Part D," which is beyond this paper's

scope.[10] This also indicates a direction for future research. As a matter of fact, whether to enroll and when to enroll cannot be separated, so that a natural extension of this work would be to model consumers' decisions by a sequential decision model where the individual first chooses *whether* to enroll and then determines *when*.

Another issue that deserves further attention is consumers' plan choice. Many aspects of consumers' rationality need to be evaluated in the context of the Part D program; this paper provides insight into only one. It is certainly of interest to policy makers to understand how consumers choose among different prescription drug plans and whether their choices change in response to market competition. Also whether consumers choose the plan that is optimal for them, given price and features of the plan compared to those of other plans, is an intriguing topic of investigation, but it requires enormously rich data to model consumers' entire choice set.

Finally, even though the landscapes of Part D insurance plans greatly changed between 2006 and 2007, very few consumers switched plans. That may suggest either a lack of elasticity on the part of consumers to market signals or a high transaction cost for switching plans. These are worthwhile for further investigation.

In sum, Medicare Part D is a social experiment about the ability of a privatized market to deliver social services. But it is also a test of the responsibility and rationality of

[10] Unlike a hazard regression framework in which each individual in the sample eventually will "die," but some of the "deaths" are not observed, right-censored respondents in this case do not necessarily enroll at the end. That also indicates a nested feature of decisions.

consumers in a consumer-directed health insurance market. The policy significance highlights the need for the research community to devote more attention to this topic.

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Appendix 1

Table 1:1 Comparison of Characteristics Between Samples Not-Missing and Missing Enrollment Time

	Enrollment time observed (N=2,700)	Enrollment time Missing (N=221)	Chi2/t stat
Demographics			
Female (%)	62.2	64.7	0.8
Age (at signup)	73.5	73.8	0.3
Education (%)			19.1
Less than High-School	24.7	37.6	
GED/HS Graduate	37.9	33.0	
Some College	20.4	18.1	
College and above	17.1	11.3	
Race (%)			18.8
White/Caucasian	88.0	77.8	
Black/African American	9.7	18.1	
Other	2.3	4.1	
Proxy interview (%)	6.7	13.6	2.9
Married (%)	60.9	49.3	-3.3
Household Wealth(median)	228,000	100,000	
Household annual income(median)	29,460	22,172	
Health Insurance			
Medical insurance plan (%)			
VA	1.0	2.3	1.3
private insurance	12.6	9.9	-1.3
Total Medical OOP last 2 years ($,median)	2,863	2,806	
Prescription Drug Insurance			
Whether Rx cost covered prior Part D			10.0
Completely covered	5.9	8.1	
Mostly covered	18.3	24.8	
Partially covered	28.1	28.6	
Not covered at all	38.1	29.0	
Average monthly Rx plan premium	34.8	37.7	0.6
Prescription Drug Utilization			
Regularly take Rx (%)	90.7	91.0	0.1
Total Medications regularly taken			6.4
Take 0	19.6	17.6	
Take 1-3	75.6	73.8	
Take 4-7	4.8	8.6	
Monthly Rx OOP prior Part D($,median)	100.0	99.5	
Take Rx for common health problems (%)	76.8	78.1	
Health			

Self-reported Health (%)			15.0
Excellent/Very good	34.7	28.6	
Good	32.7	25.9	
Fair/Poor	32.7	45.5	
Has any ADL	20.6	28.5	2.5
Ever had memory problem	6.1	12.2	2.7

Table 1:2 Prescription Drug Use and Signup Time

	Regularly take medications		Total Medications for 8 chronic conditions		
Signup time	**No**	**Yes**	**0**	**1 to 3**	**4 to 8**
2005	19.1	32.2	23.8	33.1	27.1
Jan06	19.5	21.8	20.8	21.6	24.0
Feb06	9.2	11.2	9.1	11.1	17.8
Mar06	10.8	9.4	10.0	9.1	14.0
Apr06	17.5	11.4	15.7	11.2	9.3
May06	23.9	14.1	20.6	14.0	7.8
All	100.0	100.0	100.0	100.0	100.0
N	251	2,449	529	2,042	129

Table 1:3 Out-of-Pocket Costs by Signup Time

	Rx Out-of-Pocket Prior Part D(2006)			Mean Rx Out-of-Pocket over last 5 waves		
	N = 2,669			N = 2,661		
Enrollment Time	**Mean**	**Median**	**S.D**	**Mean**	**Median**	**Within-individual S.D**
2005	200	100	536	117	94	73
Jan06	166	72	436	109	90	69
Feb06	174	100	274	122	97	74
Mar06	165	85	303	115	88	72
Apr06	115	50	204	94	81	58
May06	117	60	187	85	69	52
Total	164	75	398	108	88	67

Note: All values are monthly amounts adjusted to 2006 dollar.

Table 1:4 Signup Time by previous Coverage status

	Cost Completely covered	Cost Mostly covered	Cost Partially covered	Cost Not covered at all
2005	33.3	32.4	36.5	29.4

Jan06	28.9	28.3	19.0	19.8
Feb06	9.6	9.9	11.6	11.9
Mar06	7.7	6.0	8.9	11.4
Apr06	9.6	10.1	11.1	12.0
May06	10.9	13.2	12.9	15.4
All	100.0	100.0	100.0	100.0
N	156	484	742	1,005

Table 1:5 Health Conditions by Signup Time

	Number of Chronic Medical Conditions			Self-rated Health Conditions		
Signup time	**0**	**1-3**	**4-8**	**Excellent/ Very Good**	**Good**	**Fair/Poor**
2005	24.7	30.9	32.7	30.7	32.4	30.0
Jan06	18.0	21.3	23.3	19.0	22.7	23.0
Feb06	8.0	10.7	12.7	9.1	10.3	13.9
Mar06	10.7	9.4	9.7	9.7	8.6	10.2
Apr06	12.0	12.5	10.5	12.6	12.5	10.8
May06	26.7	15.3	11.1	18.9	13.5	12.2
All	100.0	100.0	100.0	100.0	100.0	100.0
N	150	1,911	639	936	881	881

Table 1:6 Whether Experienced Difficult and Signup Time

	How difficult to choose plan		
	Not difficult	**Difficult**	**Did not make decision myself**
2005	35.3	28.2	29.0
Jan06	22.9	20.8	23.9
Feb06	10.4	13.2	9.4
Mar06	8.7	10.8	12.3

Apr06	12.5	12.2	12.3
May06	10.3	15.0	13.0
All	100.0	100.0	100.0
N	1,220	1,094	138

Table 1:7 Summary statistics of monthly OOP by the presence of difficulties and signup time

	Whether experienced difficulties choosing plan								
	Not Difficult (N = 1,220)			Difficult(N = 1,094)			Did not make decision by myself (N = 138)		
	Mean	Median	S.D	Mean	Median	S.D	Mean	Median	S.D
2005	175	80	619	242	100	456	134	150	260
Jan06	131	70	339	199	80	564	159	100	114
Feb06	154	99	278	207	100	274	526	150	206
Mar06	169	80	285	176	95	346	128	70	166
Apr06	141	40	216	106	68	184	179	28	110
May06	80	40	117	113	70	194	257	110	90
Total	157	70	431	172	86	397	145	100	183

Table 1:8 Characteristics of Consumers who experienced and did not experience difficulties choosing plan

	No Difficulty N = 1,220	Experienced Difficulty N = 1,094	Chi2/t stat
Female (%)	58.9	67.1	4.1
Education (%)			9.0
Less than High-School	24.2	23.1	
GED/HS Graduate	35.8	41.6	
Some College	21.7	18.8	
College and above	18.4	16.5	
Total Medical OOP last 2 years ($,median)	2487.0	3131.5	
Whether Rx cost covered prior Part D			12.0
Completely covered	6.4	5.0	
Mostly covered	18.7	17.7	
Partially covered	28.0	29.5	
Not covered at all	35.9	40.1	
Regularly take Rx (%)	89.2	92.5	2.8
Total Medications regularly taken			10.9
Take 0	22.1	17.3	
Take 1-3	73.8	77.0	
Take 4-7	4.1	5.8	

Monthly Rx OOP prior Part D($,median)	70.0	90.0	
Self-reported Health (%)			18.1
Excellent/Very good	39.1	31.0	
Good	32.5	34.5	
Fair/Poor	28.4	34.4	
Has any ADL	17.1	20.0	1.8
Ever had memory problem	3.4	4.5	1.3

Table 1:9 Odered probit model with enrollment time as dependent variable (early, intermediate and late signup)

	Unweighted sample			Weighted sample		
	Sample (1)	Sample (2)	Sample(3)	Sample (1)	Sample (2)	Sample(3)
Ln(Monthly OOP)	-0.06***	-0.08***	-0.08***	-0.06**	-0.08***	-0.08***
	(-2.66)	(-4.22)	(-4.22)	(-2.50)	(-3.96)	(-3.96)
OOPSTD: 1st Quartile	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-
OOPSTD:2nd Quartile	0.03	0.05	0.05	0.02	-0.01	-0.01
	(0.26)	(0.47)	(0.47)	(0.18)	(-0.13)	(-0.13)
OOPSTD:3rd Quartile	0.00	0.05	0.05	-0.04	-0.02	-0.02
	(0.01)	(0.71)	(0.71)	(-0.41)	(-0.20)	(-0.20)
OOPSTD:4nd Quartile	-0.14*	-0.11*	-0.11*	-0.15*	-0.14*	-0.14*
	(-1.89)	(-1.77)	(-1.77)	(-1.68)	(-1.85)	(-1.85)
Rx cost completely covered	-0.48***	-0.60***	-0.60***	-0.52***	-0.63***	-0.63***
	(-3.08)	(-4.65)	(-4.65)	(-2.98)	(-4.36)	(-4.36)
Rx cost mostly covered	-0.25***	-0.23***	-0.23***	-0.25***	-0.21***	-0.21***
	(-3.45)	(-3.61)	(-3.61)	(-3.08)	(-3.09)	(-3.09)
Rx cost partially covered	-0.14**	-0.19***	-0.19***	-0.14*	-0.19***	-0.19***
	(-2.13)	(-3.57)	(-3.57)	(-1.91)	(-3.12)	(-3.12)
not regularly take Rx	-0.07	-0.12	-0.12	-0.12	-0.20	-0.20
	(-0.50)	(-1.00)	(-1.00)	(-0.76)	(-1.49)	(-1.49)
Rx cost not covered at all	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-
Difficult to make decision	0.24***	0.23***	0.23***	0.21***	0.23***	0.23***
	(4.47)	(5.00)	(5.00)	(3.51)	(4.50)	(4.50)
Did not make dicision myself	0.06	0.18*	0.18*	0.05	0.17*	0.17*
	(0.53)	(1.88)	(1.88)	(0.39)	(1.69)	(1.69)
Not difficult to make decision	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-
Health:Excellent/Very good	0.06	0.07	0.07	0.03	0.05	0.05
	(0.95)	(1.26)	(1.26)	(0.50)	(0.82)	(0.82)
Health: Good	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-	-Ref-
Health:Fair/Poor	0.04	0.03	0.03	0.04	0.06	0.06
	(0.58)	(0.59)	(0.59)	(0.52)	(0.91)	(0.91)
LL	-3217	-4494	-4494	-3095	-4350	-4350
Chi2	86	187	187	66	128	128
DoF	27	27	27	27	27	27

N	1903	2700	2700	1830	2608	2608

* p<0.1, ** p<0.05, *** p<0.01

Figure 1:1 Part D Consumer's Payment and Net Benefit in 2006

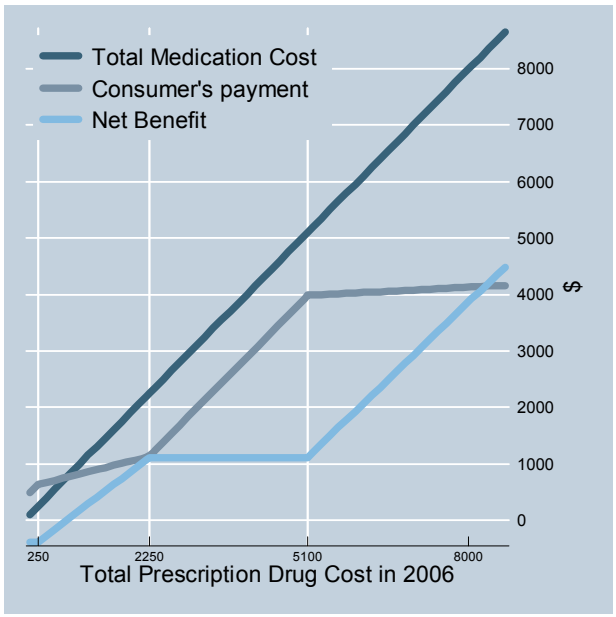


Figure 1:2 Consumer's Total Cost by Different Enrollment Time

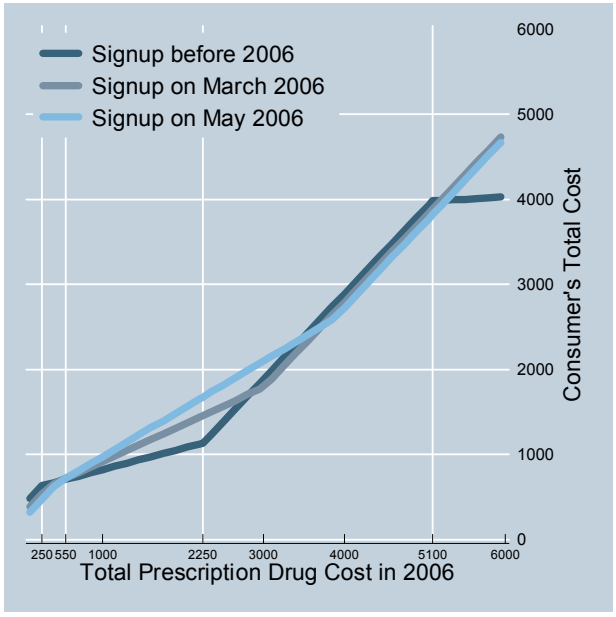


Figure 1:3 Consumer's Adjusted Total Cost by Different Enrollment Time

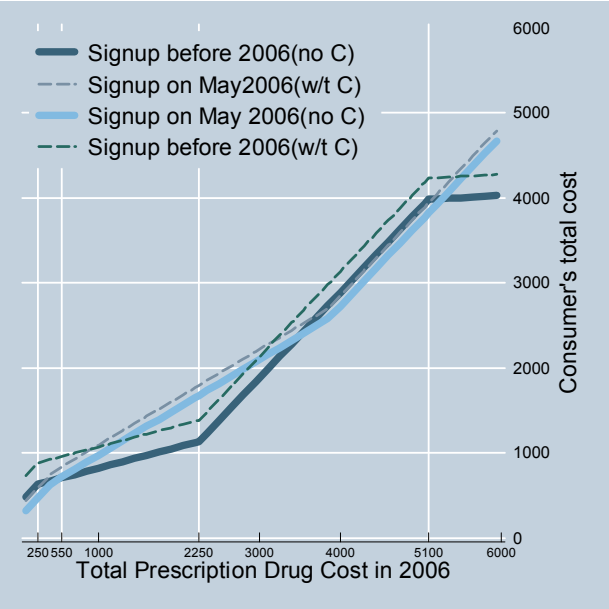


Figure 1:4 Distribution of Enrollment Time

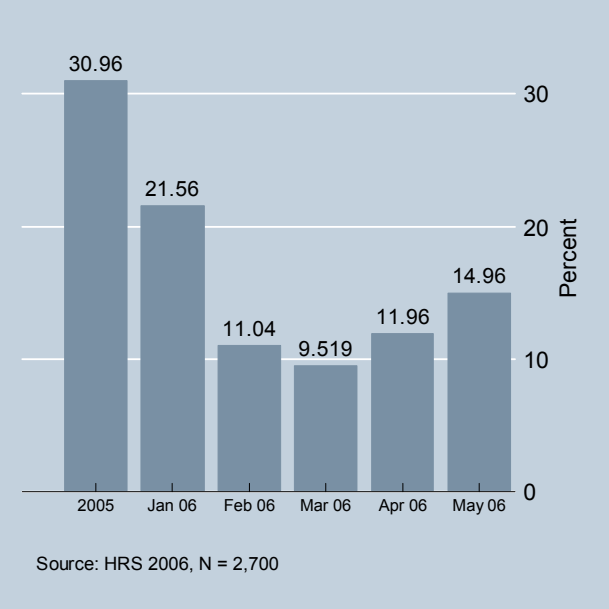


Figure 1:5 Cumulative Distributions of OOP prior Part D

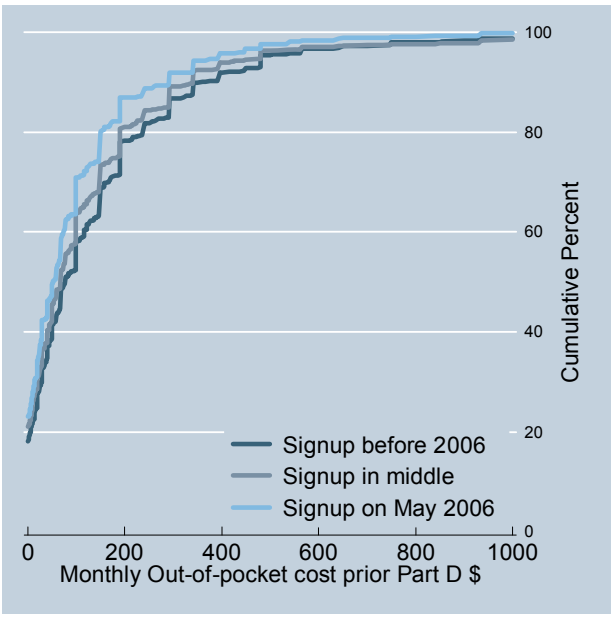
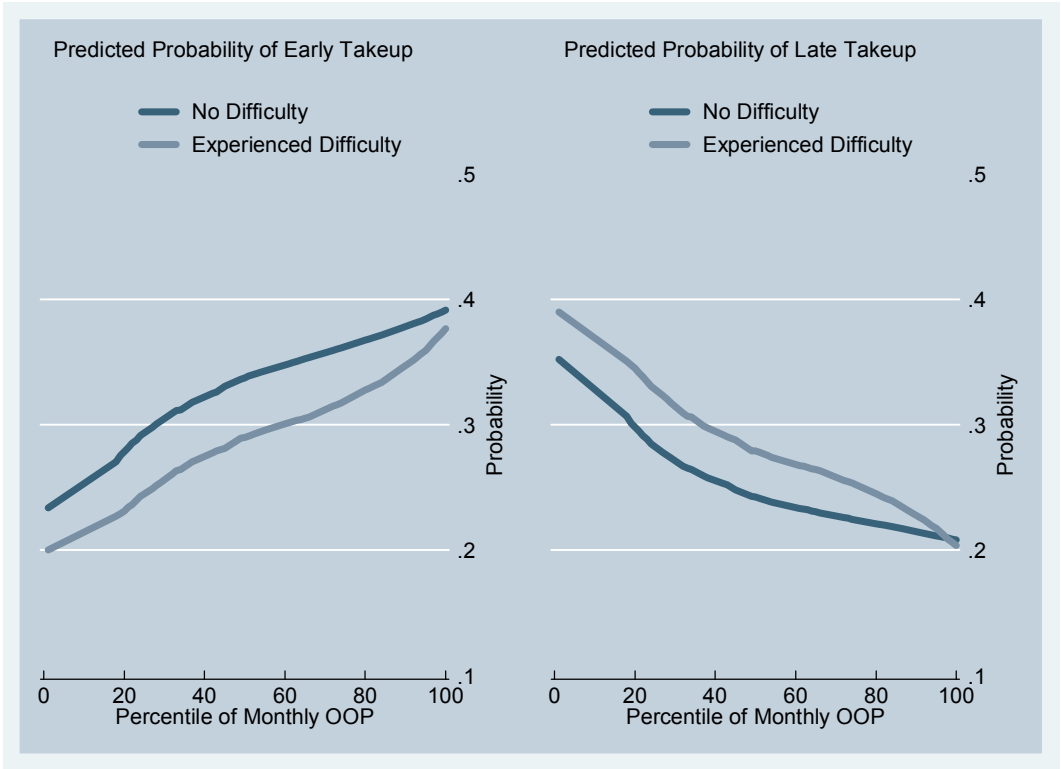


Figure 1:6 Predicted Probabilities of Enrollment by Prior OOP Cost



Chapter 2 A Simulation Model to Evaluate the Cost and Effectiveness of Alternative CKD Intervention Strategies

Abstract

One in eight Americans is now living with Chronic Kidney Disease (CKD). The CKD burden in US is expected to increase in the coming years due to the rising prevalence of hypertension, diabetes, obesity, and the growth of elderly population. CKD causes premature morbidity and mortality and lowers quality of life. It is also an expensive disease to treat. The large economic burden and adverse health outcomes of end-stage renal disease can be prevented by early detection and treatments. However, those interventions are being delivered inadequately to improve population-based outcomes. Based on existing literatures, it is also unclear whether the early interventions are cost-effective. The proposed study aims to address that question based on an analytical simulation model.

The simulation model is a Markov model with different CKD stages and death as transition states. It simulates the changes of health states in individual's life history over the next 20 years. During this period, people can maintain their health, develop CKD and progress to severer stages, encounter its comorbidities, or die. Simultaneously, they can develop risk conditions, such as hypertension and diabetes, which accelerate their CKD progression. Demography and treatment also influence the probability of the disease occurring or progression to advanced stages. The changes of health status are determined

by the transition probabilities collected from clinical evidences and they will be updated at every time step by current health status. Within the general conceptual model I distinguished 3 sub-models: a module simulating CKD risk conditions: hypertension and diabetes, a module for the course of CKD progression, and the module for cardiovascular disease as the major comorbidity of CKD. The simulation model is designed to simulate a cohort of a nationally representative sample over time. In the model, the incidence, prevalence, death, and costs associated with the health conditions are tracked and summarized at each year. The outputs of the model will be 20-year health outcomes, utilization and costs for the simulated cohort of the US adults.

Introduction

The escalation of CKD to an urgent matter of public health concern is a consequence of the current and anticipated disease burden on the American population. The burden of CKD underscores the need for improved detection, treatment, and monitoring of clinical and fiscal outcomes. Many studies devote efforts to the study of treatments on End-Stage Renal Disease (ESRD), but the upstream strategies are largely overlooked. To objectively evaluate the potential health and economic consequences of upstream intervention to prevent CKD, especially ESRD, it is necessary to understand the full spectrum of CKD and intervention effects. Ideally cost effectiveness evaluation would be based on randomized trials that compared the interventions against what happens in the absence of interventions. However, an adequate trial that meets this objective does not exist. Simulation modeling, an analytic methodology which is based on data drawn from primary and/or secondary sources, is therefore useful to inform the decision-making under the circumstance.

Simulation modeling has been used widely in economic evaluations of pharmaceuticals and other health care interventions. It is a logical mathematical framework that synthesizes evidence on health consequences and costs from many different sources, including data from clinical trials, observational studies, and public health statistics. The purpose of modeling is to structure evidence on clinical and economic outcomes in a form that can help to inform decisions about clinical practices and health-care resource allocations. Simulation can be operated both at macro and micro level. Microsimulation models are models that operate at the level of the individual behavioral entity. Such

models simulate large representative populations of these low-level entities in order to draw conclusions that apply to higher levels of aggregation such as an entire country. This type of model is distinct from macro-level models whose explanatory variables already represent groups of all entities with given properties.

In this paper, we present a simulation model developed as the basis for estimating the cost and effectiveness of interventions to reduce the burden of CKD. This is a comprehensive model that considers all stages of CKD, the CKD risk increasing conditions, major complications and comobidities of CKD. The model is based on the best-available evidence regarding the prevalence of chronic kidney disease in U.S and the effectiveness of CKD management. The studied sample is representative of the national population so the simulation results can be generalized nationwide. The comprehensive model allows the evaluation of the interventions not only at the level of the population eligible for the intervention but also at total population level over time and by age, sex, and race ethnicity. It also allows us to evaluate different interventions affecting CKD within the same, consistent analytic framework and to inform prioritization of different interventions. In order to implement the model we apply the technique of microsimulation. The model generates a large number of individual life histories, concentrating on the aspects of development of the disease that may be interesting from a particular policy question. Together, the life histories of the population of interest are the basis for all results.

Pathological Mechanism of CKD Development

Chronic kidney disease (CKD), also known as chronic renal disease, is a progressive loss of renal function over a period of months or years. CKD begins with an initial loss of nephrons through injury, inflammation or hypertensive scarring, with this initial insult usually followed by a decline in GFR (Remuzzi and Bertani, 1998). It has been suggested that excessive filtering and reabsorption of proteins by the kidneys, under a situation of elevated glomerular pressure, leads to an inflammatory reaction and ultimately to renal scarring (Remuzzi and Bertani, 1998). Hence, while proteinuria (or albuminuria) is often the first sign of progressive kidney damage, it might also be a mechanism of progressive kidney disease. More severe proteinuria is associated with faster disease progression (Adler, et al., 2003). Loss of kidney function usually takes place gradually over many years, and often loss of kidney function has neared terminal stages before a person experiences significant symptoms. End Stage Renal Disease (ESRD) is reached when the kidneys have too few functional nephrons left to maintain normal electrolyte and water balance. At this stage, dialysis or a kidney transplant are required to live. Whether or not an individual reaches ESRD depends on the type of primary kidney disease, how well this disease and associated risk factors are managed, and the presence or absence of other risk factors and comorbid conditions.

Hypertension and diabetes have a strong and causative association with CKD. Hypertension forms part of the pathological mechanism by which CKD is initiated, and is also a consequence of reduced kidney function. The kidneys regulate blood pressure by varying the amount of sodium and water excreted to maintain a homeostatic level. As

CKD evolves, the kidneys' capacity to maintain blood pressure homeostasis declines progressively. For this reason in almost all cases of CKD, rising blood pressure occurs concomitantly with progressive decline in kidney function. At the same time, hypertension and CKD promote arteriosclerosis, potentially leading to aggravation of the underlying kidney disease at the level of large (renal artery stenosis) and small vessels (hypertensive nephrosclerosis). Population studies have shown that progressive increases in blood pressure are associated with progressive increases in risk of ESRD. Elevated blood sugar levels in diabetes, if uncontrolled, can lead to microvascular damage as well as kidney damage. Chronic hyperglycaemia and the associated disturbances of carbohydrate, fat and protein metabolism cause permanent damage to kidneys (Ritz and Orth, 1999). Kidney function naturally declines with age therefore older persons are at greater risk of developing CKD than younger. In the Framingham Offspring study, the odds of developing CKD more than doubled with every 10 year increase in age (Fox, et al., 2004). Many ethnic groups experience a higher prevalence of CKD and ESRD than surrounding populations. Many of the risk factors for CKD are modifiable, such as diabetes, hypertension, obesity and smoking. Other non-modifiable risk factors, such as older age, ethnicity and family history, might be useful to indicate high-risk individuals for opportunistic screening in primary care.

Complications of CKD develop in the early stages of disease and are often well advanced by the time CKD is diagnosed (Johnson, 2004). The key health consequences of CKD are: (1) progression to end-stage renal disease requiring dialysis or kidney transplantation to sustain life; (2) premature cardiovascular disease causing death or morbidity; and (3)

complications of CKD including hypertension, anaemia, bone disease, impaired reproductive functions and diminished quality of life.

Literature

Several models that evaluate interventions affecting CKD already exist but they tend to concentrate on one or some closely related interventions on the End-Stage Renal Disease population (Arredondo, et al., 1998; Chang, et al., 2004; Gonzalez-Perez, et al., 2005; Karlberg and Nyberg, 1995; Klag, et al., 1997). These studies show that renal transplant offers the least expensive alternative and the greatest number of years of life gained as well as providing significant changes in the quality of life of ESRD patients.

Few studies conduct economic evaluation of the early detection and prevention of CKD. Hendry et al. developed an economic model to analyze the cost impact of ACE inhibitor treatment on progression to ESRD in diabetic patients over 4 years. Two scenarios were compared: one describing the progression of a cohort of 1000 patients receiving 25 mg captopril three times daily, and the other for an equivalent cohort without such prophylactic treatment. Previously published data were used to estimate the transition rates for each stage from the onset of renal failure until death. The discounted cost saving of ACE inhibitor treatment for a cohort of 1000 patients was estimated as 0.95 million pounds over 4 years. Prophylactic treatment with ACE inhibitors was predicted to provide substantial increases in life expectancy and reduction in the incidence of ESRD, while also providing significant economic savings (Hendry, et al., 1997). Using clinical data obtained from a 3-year randomized clinical trial [the Angiotensin-Converting-

Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study], Hogan et al. developed a four-state Markov model to evaluate the effectiveness of benazepril on slowing the CKD progression. In the clinical studies on which this economic analysis was based, patients with chronic renal insufficiency of various aetiologies were randomised to antihypertensive therapy with or without concomitant benazepril. Over 7 years of analysis, patients randomized to antihypertensive treatment with concomitant benazepril therapy incurred on average USD12991 (1999 values) lower medical costs than patients prescribed antihypertensive treatment without benazepril, and obtained an additional 0.091 quality-adjusted life years (QALYs). Costs and QALYs were greater for the benazepril arm than the placebo arm for all years of analysis. Benazepril therapy as a component of antihypertensive treatment of persons with chronic renal insufficiency initially costs money, but investment costs are recouped quickly and return on investment continues to grow(Hogan, et al., 2002). In a more recent study, Boulware et al accessed the value of periodic, population-based dipstick screening for early detection of urine protein in adults with neither hypertension nor diabetes and in adults with hypertension. They used a Markov decision analytic model to compare a strategy of annual screening with no screening for proteinuria at age 50 years followed by treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II-receptor blocker (ARB). For persons with neither hypertension nor diabetes, the cost-effectiveness ratio for screening versus no screening (usual care) was unfavorable. However, screening such persons beginning at age 60 years yielded a more favorable ratio. For persons with hypertension, the ratio was highly favorable. They concluded that early detection of urine protein to slow progression of chronic kidney disease and decrease mortality is not cost-

effective unless selectively directed toward high-risk groups (older persons and persons with hypertension) or conducted at an infrequent interval of 10 years(Boulware, et al., 2003).

A more closely related study is a simulation model developed by Lee et al to estimate the cost and effectiveness of alternative dialysis initiation strategies. Their model generates hypothetical patient cohorts and simulates the disease progression to ESRD among each cohort. Instead of modeling the progression over different CKD stages, they simulated several adverse health events such as ESRD, dialysis, transplant and graft failure, hospitalization and death. The model aims to establish an analytical framework to derive the optimal timing of dialysis initiation in terms of cost-effectiveness (Lee, et al., 2006).

Most of the existing models used in these studies rely on some form of macro-simulation which implies that the model represents the characteristics of individuals as fractions of the total modeled population. The problem of an infinite number of different possible individuals that can occur and need to be considered is handled by assuming granularity, in particular continuous time is reduced to a limited number of time steps. As long as the number of population fractions that need to be modeled remains within reasonable limits, this technique will be sufficient and computations of the model will be fast. A comprehensive model as proposed here would require a very large number of population fractions that need separate administration in the computer model, requiring an extremely complex algorithm. That makes the alternative of microsimulation more viable. In microsimulation the problem of an infinite number of different possible individuals is

handled by sampling instead of granularity. The main disadvantage of microsimulation or sampling is random error in the results. Fortunately, increasing the number of microsimulated life histories requires much less effort than increasing the sample in an empirical study of human subjects therefore we can reduce random error to much smaller proportions than in empirical studies. Additionally, microsimulation model offers closer comparisons with empirical studies and validation than macrosimulation. However, when the analysis requires a large number of model evaluations, each requiring a large sample of life histories, micro-simulation can be slow.

Model Architecture

We created a Chronic Kidney Disease Model to simulate the natural history of the CKD and its epidemic among adult Americans. It is a micro-simulation model to forecast the incidence, cost and health outcomes of chronic kidney disease (CKD) under varying scenarios for the U.S. adult population. We start with a nationally representative (on both demographics and health status) sample, based on weighted 1999-2002 data from the National Health and Nutrition Examination Survey (NHANESIII) and the United States Renal Disease System (USRDS). The model predicts the changes of health states in each individual's life history over the next 20 years. We simulated one cohort so no new population enters over the period of time in the model. Therefore, no new 18 year olds come into the analysis, and the model just follows the experience of the starting cohort. We chose this design because the overwhelming majority of serious outcomes in adult chronic kidney disease occurs in people over 37. During this period, people can maintain their health, develop CKD, its comorbidities, and its risk-increasing conditions, or die. The life history in the model is demonstrated in figure 1. Individuals in the model can

start from any block of the three: disease free, risk conditions or chronic kidney disease, and then experience other health events and die at the end. The model is based on the assumption that the natural history of chronic kidney disease and its complications and comorbidities can be described by a series of discrete health states that represent the progression of kidney function decline.

Within the general conceptual model we distinguish 3 sub-models describing the changes in three major dimensions of health states of interest: a module for the course of CKD from CKD free through stage 5, a module for the incidence and prevalence of CKD risk-increasing conditions (hypertension and diabetes), and the module for death and the incidence of Cardiovascular Disease (CVD), which accounts for more than 60 percent of CKD death.

The CKD Transition Module (see figure 2) is the core module of the model, which describes CKD progression from CKD free to End Stage Renal Disease (ESRD) with the presence of albuminureia and the decline of estimated Glomerular Filtration Rate (eGFR). The model is a Markov process with different CKD stages and death as transition states. Individual's health states advance at the time step of one year except stage 4 CKD and ESRD. Treatment, risk conditions, and demography influence the probability of the disease occurring or progressing to higher stages. In the model people do not recover from ESRD unless they receive a renal transplant.

Stage 4 CKD and ESRD have a significant negative impact on quality of life, and are associated with increased mortality, and health care needs. Furthermore the eGFR declines at a much faster rate than it is in early stages, as well as the presence of comobidities. We developed two sub-modules for those two stages within the model. Once individual moves from stage 3 to stage 4 or ESRD the time step changes to one quarter within those two sub-modules. In those modules, dialysis and transplant are an additional influence on disease progression and health care costs, and transplantation can lead to recovery from ESRD.

The Risk Conditions Module (see figure 3) describes the incidence of the two most relevant risk conditions (diabetes and hypertension), which are influenced by age, sex, and race/ethnicity. The incidence of hypertension is also affected by CKD stage, but diabetes is assumed independent of CKD. Individual can experience either one condition or have both risk conditions. The chronic conditions are persistent and incurable in the model but can be controlled through treatment. Control reduces their impact on CKD progression and Cardiovascular Disease.

The Death and Comorbidity Module describes non-CVD death and the incidence and death from Cardiovascular Disease as a comorbidity of CKD-caused death. The risk conditions and CKD severity as well as other demographic factors affect non-CVD mortality and the occurrence of CVD event and the probability of resulting death. The two modules above are connected to this module to implement these events. The CKD stage transition probabilities in each of the steps are influenced by demography, risk

conditions and treatment. We obtained the probabilities by an extensive review of existing literature and from NHANES III. These parameters and the methods used to calculate them are described in model parameter section.

Comprehensive CKD prevention and treatment programs can be considered in the model, which allows us to evaluate interventions not only at the level of the population eligible for the intervention but also at total population: split out by different stages and by age, sex, and race/ethnicity. Furthermore, given the consistent analytic framework, we are able to validly compare different interventions for prioritization.

Cost and Utility

We collected the parameters of costs and utilities from published literatures. The direct medical cost of CKD treatment is obtained from an economic evaluation by Hogan et al (Hogan, et al., 2002). In their estimates, they reported the cost by CKD stages. The costs of dialysis, renal transplantation and post-transplant maintenance care were also estimated from the United States Renal Data System (USRDS). In additional to the annual medical cost, we used the estimates from Hodgson et al as the direct medical cost of cardiovascular disease event (Hodgson and Cai, 2001). The cost is discounted into the 2008 dollar. Health utilities measure the decline in health related quality of life due to functional limitations and discomfort. Health utility scores range from zero to one, where zero represents death and one represents perfect health. They are affected by age and disease. Health utilities employed in the model were determined by analytical estimates based on reference to the quality-of-life literature (Anis, et al., 2006; Boulware, et al.,

2003; Brown, et al., 2000; Hogan, et al., 2002). The progression of disease results in a decrease in the health utility scores. Health utility scores for ESRD were further adjusted by the status of transplantation. Quality adjusted life years (QALYs) are calculated by multiplying the utilities of various health states and the lengths of time individuals spend in them.

Consistent with existing literature, the present value of both cost and quality-adjusted life years were discounted by 3% per year. The incidence, prevalence, death and costs, health utilities associated with the health conditions are tracked at each year and summed at the end. We then report total years lived, years lived in each stage, discounted years lived and quality adjusted discounted years lived.

The simulation is implemented at micro level. Figure 4 gives an overview of the architecture of the model. The model begins with a nationally representative sample of individuals age 18 and older in year 2000. In the model individual can experience different disease path in her life history. She can experience no disease, one single disease, or any combination of the diseases of concern. The model advances individual's health states in one year steps for CKD free and stage 1-3 people. In stage 4 and stage 5, the time step becomes one quarter of a year, reflecting the faster rate of change and greater impact of events. At each time step, the occurrence of the disease event is a stochastic Markov (first-order) process.In order to facilitate comparison of model scenarios and optimize interventions, we implement variance reduction to reduce the random error of differences between scenarios that is due to stochasticity of the model. For example, without variance reduction, when comparing two intervention scenarios in a

simulated population where the expected number of ESRD cases under scenario 1 is 1000 and under scenario 2 is 1100, then the expected difference of 100 cases has a Poisson variance of 1000 + 1100 = 2100. With variance reduction, life histories are only different from the time that the different intervention affects the life history. The same 1000 cases that would get ESRD under scenario 1 also get the disease under scenario 2 and only the 100 extra cases are changing with respect to acquiring ESRD. Therefore the variance of the difference between scenario 1 and 2 is not 2100 but only 100.

Monte Carlo techniques are used to implement the disease progression. At each time step, a uniform random number between zero and one is generated and is compared with the transition probability for progression from the current health state to the subsequent health state. If the random number is less than or equal to the transition probability the transition occurs and is irreversible except treatments intervene. The transition probabilities depend on the demographics, the current health states and treatment.

Model Variables

The variables in the model include the demographics and the health states of each individual. The demographics characteristics of each individual are gender, race/ethnicity and age. Health state variables include CKD, hypertension, diabetes, cardiovascular disease and so on. In the model, the race/ethnicity is defined as Hispanic, Non-hispanic white, Non-Hispanic Black, and other race. Health state variables are defined as follows.

The CKD variable is defined by glomerular filtration rate (mL/min/1.73 m2) and the albumin-to-creatinine ratio. To calculate glomerular filtration rate (**GFR**), we used the formulas of the National Kidney Foundation[11]. Using the glomerular filtration rate and albumin-to-creatinine ratio, we created the following variable for the different stages of chronic kidney disease. In the model, we combine stage 1 and stage 2 because in practice the therapies and the resulting medical costs for these two stages are not significantly difference. [table 1]

The hypertension variable is defined by two variables measured in NHANES: 1) whether you were diagnosed with hypertension; and 2) the systolic and diastolic blood pressures. Individual is hypertension free is she reported never been diagnosed hypertensive. In the current version, we do not model the diagnosis or screening of risk condition so we ignore the undiagnosed cases of hypertension and diabetes in NHANES III (about one third of hypertensive patients are unaware of their condition(Hodgson and Cai, 2001)). Individual has controlled hypertension if she was diagnosed as hypertensive and the systolic blood pressure is lower than 140 and diastolic blood pressure is lower than 90. An individual has uncontrolled hypertension if she was diagnosed as hypertensive and the systolic blood pressure is higher than 140 or diastolic blood pressure is higher than 90.

The diabetes variable is defined similarly. We classify diabetes status as three outcomes: diabetes free, controlled diabetes and uncontrolled diabetes. The classification is based on doctor's diagnosis and the glycohemoglobin level. The diabetes condition is controlled if HbA1c level is lower than 7 and uncontrolled if it is equal to or higher than 7.

[11] http://www.annals.org/cgi/reprint/130/6/461.pdf, accessed on March 1st, 2009.

Model Parameters

There are four sets of parameters in the model: CKD transition probabilities, the incidences of risk conditions, mortalities, and the parameters which control the relationships among diseases. All the parameters are adjusted by gender, race/ethnicity and age. The parameters come from both published literatures and our estimations based on observational data. We present the methods employed to estimate the core parameters in the model, which are the CKD transition probabilities. For transitions from stage 3 to stage 4 there is a reasonable literature, but not much on earlier stage and stage 4 to stage 5 transitions. Due to the limited evidences, we use prevalence data from NHANES and USRDS to estimate the transition probabilities from CKD free to CKD stage 3 and stage 4 to stage 5.

Early stage CKD transition probabilities

In our model stages 1 and 2 are combined, so we have three states: stage 0 (healthy), stage 1&2, stage 3. We need to estimate annual transitions from stage 0 to stage 1&2, from stage 0 to stage 3, and from stage 1&2 to stage 3. We assume the reverse transitions to healthier stages zero, so we are estimating the net transitions. In addition, we will estimate death for these 3 groups. It will be useful in estimating transitions into stage 3 to separate those people whose GFR is close to 59, so we have four bins, splitting both stage 0 and stage 1&2 into those with GFR>74, and those with GFR 60-74. The 4 bins will be called 0H, (where the H stands for High GFR), 0L, 1&2, and 3.

We break down the sample by race and gender groups and repeat the following calculation for each of the six gender race groups. We first divide the sample into only 6 age categories (18-39, 40-49, 50-59, 60-69, 70-77, 78+) to ensure estimates of prevalence of each CKD stage follows age smoothly. And then we subdivide these categories into 13 5 year age categories. So we start with 13 age categories and 4 CKD stage bins. People will enter the higher bins as they get chronic proteinuria, or their GFR drops below 60.. They will enter or leave them as their GFR declines, or die. At the same time they are aging. The method calculates what has to be true for the transitions for stages to be in equilibrium. We assume that people transition to stage 3 in one year only from bins 0L and 1&2 (i.e. no massive declines in GFR). People transition to stage 1&2 only from stage 0, based on the rate of developing kidney damage, and they either switch from 0H to 1 or from 0L to 2. We also use an estimate from the literature that GFR declines by 0.8 per year for people without proteinuria(Johnson, 2004).

Take a subgroup where people have age 40-44 and GFR ranges from 60 to 74 with proteinuria (stage 2) as an example. The people transitioning in were either 39 and already in 2 or else they were 39-43 in the preceding year and either were in 0L: GFR with 60-74 and no proteinuria, or they were in group 1: GFR 75+ with proteinuria. (This transition group is quite small as the range of GFRs in 1 goes from 75-125, and so a shift of .8 in GFR would bring in only 2-3% of a category, Stage 1&2, that is small until people get fairly old.) People transitioning out include everyone who was 44, plus those 40-43 who died, or who shifted to stage 3. In steady state these inflows and outflows will cancel. In the calculation, we keep track of the net flows, and optimize the transition

parameters governing the flows to minimize the net flows for all cells. So, Net Flow = $-\sum X_{a,2}(-D_{a,2} - T^3_{a,2}) + (X_{39,2} - X_{44,2}) + \sum (X_{a,1} T^2_{a,1} + X_{a,0L} P_{a,0L})$, where $X_{a,s}$ is the people of age a in stage s, and a ranges from 39 to 43. D stands for death. $T^3_{a,2}$ is the people of age a in stage 2 who transition to stage 3. Similarly $T^2_{a,1}$ is the people of age a in stage 1 who transition to stage 2. We have similar equations for all the subgroups, except that stage 0 has no inflows. Deaths D for each age bin come from national averages for the race and gender. They are adjusted using a multiple based on stage: as shown they are assumed to be .9, 1.5 and 2.0 times the overall death rate for a given age for white males. The 2.0 comes from some literature on stage 3 mortality, the 1.5 for stage 1&2 is an extrapolated guess, and the .9 for stage 0 is picked to make the model total match the national data total. Incidence of chronic proteinuria P_a is assumed to increase with age.

The probability transitions due to falling GFR from 60-74 → 59, are related to the width 15 of the GFR interval and the estimated 0.8 per year decline. If people's GFR were evenly spread from 60 to 74 then 1/15 of the bin would be at 60, ready to go to stage 3. Transitions are smaller than .8/15 for young people because there are more people at the 74 end at the interval than at the 60 end where the transitions occur. In the model we increase the probability of transition as people age, and their GFR become more evenly spread from 60-74.

Hypertension Incidence

We model the hypertension as a simple three states Markov process. Individual can change from hypertension free to hypertension by developing either controlled

hypertension or uncontrolled hypertension over time with certain transition probabilities. Once an individual develops hypertension, she will keep the chronic condition over life time. However, the condition can be controlled with appropriate intervention. In the current model, the transition probabilities are the function of race, gender, age and CKD stage. The chronic disease is assumed irreversible in the model but can be controlled by appropriate treatments. The estimate of the transition probabilities is based on Vansan et al (2001). In their paper, Vansan et al did not classify the type of hypertension, but estimated the incidence of hypertension instead. To obtain the incidences of controlled and uncontrolled hypertension, we applied the proportion of the prevalence of the two types of hypertension, which was estimated from NHANES III. Table 2 and 3 show the incidences of two types of hypertension by age group, race and gender. [table 2, 3]

Diabetes Incidence

Similarly we model the diabetes as a three state Markov transition. People can develop either controlled or uncontrolled diabetes during her life history. In the model, the incidence is a function of age, race and gender, but independent of other diseases. The transition probabilities were obtained from CDC's estimate. We applied the same rule to calculate the incidences for controlled and uncontrolled diabetes. The table 4 and 5 show the diabetes transition probabilities by race, gender and age groups. Similarly the development of diabetes is assumed irreversible but can be controlled by treatments. [table 4, 5]

Death and Comorbidity

In the model we specify three mortality rates: CVD death, CKD death and other-cause death. CVD mortality and other-cause mortality are obtained from CDC cause-specific mortality table[12]. 1) We use the item of "Major cardiovascular diseases" (ICD-9 code: I00-I78) as the CVD-cause of death rate. 2) For other-cause death, we firstly calculate the general mortality using Census 2000 life table, and then subtract the general mortality with two cause-specific mortalities which are specified separately in the model: CVD mortality(ICD-9 code: I00-I78) and renal diseases mortality (ICD-9 code: I10, I12,13) and renal failure (N17-N19). 3) CKD mortality in the model is calculated as the average mortality rate of CKD patients which accounts for the death from the CKD complications except CVD. For ESRD mortality, we use the estimates by Dong et al. Dong et al estimated the annual ESRD mortality and we translated the annual mortality into quarter mortality[13]. The mortalities of CKD stage 1 to stage 4 patients come from O'hare et. al(O'Hare, et al., 2006). As a simplification, we specify CVD as the only comorbidity of CKD. The incidence of CVD event is estimated from the San Antonio Heart Study (Mitchell, et al., 1991) and the rate is assumed same for white and non-white population. The assumption is made based on the study of Hozawa et al. Their finding suggests the CVD of white and non-white are not significantly different after adjusting for the difference in hypertension and diabetes (Hozawa, et al., 2007).

Risk adjustment

[12] National Center for Health Statistics. Death Rates for 113 Selected Causes by 5-Year Age Groups, Hispanic Origin, Race for Non-Hispanic Population, and Sex: United States, 1999-2004. http://www.cdc.gov/nchs/data/dvs/Mortfinal2003_worktableOrig291r.pdf. Accessed on August 10, 2008.

[13] The quarterly mortality rate is calculated as: $q = 1 - (1 - a)^{1/4}$ where a is annual rate and q is quarter rate.

All the transition probabilities are adjusted by demographics: race, gender and age. The age and sex differences in the incidence of CKD across race/ethnicity groups are reflected in the initial distribution of the sample. In addition, the mean race/ethnicity differences in CKD progression are incorporated in the model input. African American population is shown a higher CKD stage transition rates. Race/ethnicity also affects mortality rate from ESRD and other causes. Some of the probabilities are adjusted additionally by other health conditions. For example, the incidence of hypertension is also adjusted by individual's current CKD status.

Data

The model requires a nationally representative sample with current joint distribution of CKD, risk conditions and other comobidities as the starting population. A combination of NHANES and USRDS can form the basis of the starting population. NHANES is a continuous survey of the health and nutritional status of the U.S. civilian noninstitutional population. The data is released in 2-year increments. We use a combined data from three survey periods: 1999-2000, 2001-2002, and 2003-2004. NHANES is large enough for good estimates of the composition of CKD stage 1, stage 2 and stage 3 population, but not of the rarer late stages (stage 4 and stage 5) Although it can be weighted to a national sample, with only 72 eligible people in the three waves. Therefore, we constructed the stage 4 and ESRD population using USRDS instead. USRDS is a national dataset that collects information about all people with End-Stage Renal Disease in the United States. We generate a sample of ESRD by sampling 1.5 percent of the USRDS prevalence file of year 2000 and assign each individual a weight of 70 (=1/0.015). CKD stage 4 sample

comes from the incidence to stage 5 of year 2000. We estimated the stage 4 to stage 5 transition probabilities for four race/gender sub-groups. From NHANES, we calculated the weighted numbers of people in each of the four sub-groups in stage four. Because the people are so few in NHANES, we replace them by a sample of the corresponding USRDS incidence cases. Specifically we randomly sample the number from the incident cases in each sub-group. For example the unweighted number of individual younger than 65 in stage 4 is and the weighted number is 89,491 in NHANES, we would randomly sample 89491/100 = 895 people from incident ESRD cases in USRDS who are younger than 65. They would each have weight equal to 100. The number of cases in each stage in the initial simulation cohort and the average number of US adults each one represents are given in Table 6.[Table 6]

Early stage CKD (stage 1 to stage 3) is much more common than advanced stage CKD (stage 4 and stage 5). And the progression over the early stages is relatively slow. However, CKD4 and end stage CKD are rare events but they have large economic and health consequences. The renal function at advanced stages declines much faster than early stage CKD. So in our model, there are competing goals of having enough detail on the rarer severe stages of kidney disease and having models run quickly. Our solution is to oversample later stage people and give them smaller weight. For early stage CKD transition, the time step is set to 1 year. But for advanced stages, we model them at 3 month time-step. To balance the weights as the model generates life histories, we make three copies for each individual when they transition into ckd4. By that way, we increase

the sample of advanced stage CKD in the model and reduce the randomness in these critical stages.

The initial sample is 18 years and older. If individual is older than 85 their ages are top coded as 85 and older in NHANES. Among the initial sample, 16.1 percents had chronic kidney disease. The distribution of stage-specific CKD is demonstrated in table 6. 29.3 percents had hypertension, with 18.4 under control and 11 uncontrolled. 6.3 percents had diabetes, with 2.3 under control and 4.2 uncontrolled. Table 7 exhibits the demographics and initial distribution of health conditions among the sample. [table 7]

Model Outputs and Validation

The outputs of the model are 20-year health outcomes, utilization and costs for the initial cohort of US adults with status quo treatment patterns and the incremental effects on these dimensions of various hypothesized programs. The 20 year period could be extended to 40 year outcomes by matching 20 year survivors to similar people at the start and assuming their next 20 years experience would be the same. Our model in current form calculates what would happen in the absence of technical progress in medicine, or trends in mortality and incidence independent of the factors in the model.

We conduct the internal validation by calibrating the model against the independent national health statistics. We compare both mortalities and prevalence between model predictions and the observed data between the comparable populations to see whether the model predictions are close to what we observed among the populations of interest. First,

we calculate the 20 year mortality using the simulated cohort and compare it to the observed mortality rate in 2000. It is demonstrated in the table 8 that model prediction is close to the national vital statistics for different age groups. [table 8] Secondly we calculate the one-year mortality predicted in the model and compare it with the observed statistics. We did the comparison for year 2000-2001 and 2004-2005. As illustrated in figure 1 and 2, the mortality rates of overall population are virtually indistinguishable. The match for both white and black populations are close, with slightly worse for black population because of greater random variation due to less sample.

To ensure the prevalence estimates are comparable between years, we track only the group 38 and older over the 20 years and report the disease prevalence at each year. Both the prevalence of hypertension and diabetes increase as the average age of the cohort increases over time. [figure 3 and 4] . The comparison of the prevalence prediction with Honeycutt et al shows a slightly higher prevalence projection from our model, which is mainly due to the broader definition of diabetes in our model(Honeycutt, et al., 2003). However the patterns of the projections are quite comparable. The prevalence of CKD for group age 38 and older is presented in figure 5. Among the four race/gender subgroups, the prevalence of all stage CKD is quite stable, with a slight decline. The decline is mostly driven by CKD 1&2 which accounts for nearly 70 percent of total CKD population. Generally the simulated cohort experiences a slight increase of CKD stage 4 prevalence, for both black and white populations. CKD stage 5 among white population stays stable over the 20 years while it shows an increasing trend for black population.

Limitations

The simulation model presented in the paper is intended to provide a robust computational framework, which by capturing the key elements of CKD disease progression, can be used to estimate the cost-effectiveness of alternative intervention strategies. The simulation model synthesizes several data sources and relies on some assumptions. For example, we assume the effect of risk conditions on CKD stage transition is in a linear form. One strong assumption we made in the model is that with no interventions there is no transition between controlled and uncontrolled risk conditions (including hypertension and diabetes) for simplicity. However, they do occur both ways in real life.

Some simplifications have been made in the model in light of the tradeoff between realism and computational burden. In particular, we abstracted away certain details from the model. We concentrated on the most significant risk conditions of CKD, but some other CKD risk increasing condition such as Hyper-lipidemia is ignored. Some other comorbidities of CKD such as anemia and bone diseases are not included in the death and comorbidity module of current form. The core interest of the model is CKD transition, therefore the details of risk condition development are greatly simplified. We only categorized them into controlled and uncontrolled levels without considering further the clinical stages of these chronic conditions.

Another limitation is the sensitivity of the model to the input parameters, especially the event rate estimates. If these estimates are biased, the simulation would tend to be biased.

This is an issue inherent in any model. Therefore any analysis based on this model requires rigorous sensitivity analysis.

In summary, for chronic kidney disease, where existing data and randomized clinical trials on early intervention strategies, especially national level intervention, are lacking, simulation can serve as an informative and complementary tool for understanding the potential consequences of the strategies. By utilizing available and newly derived data and abstracting the key elements of disease progression, our model provides a comprehensive analytical framework allowing evaluations of interventions under various scenarios. Although the structure of the model has been determined, a basic strength of any model is its potential for improvement at moderate cost New data from empirical surveys or clinical trials may improve our parameter estimates or inform additional modules covering other outcomes and interactions in the next iteration of the simulation model.

Acknowledgement: The initial support for this paper has come from the Charles Drew University/RAND/UCLA Comprehensive Center for Health Disparities in Chronic Kidney Disease U54 RR019234 NCRR/NIH.

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Appendix 2

Figure 2-1 Top level conceptual model

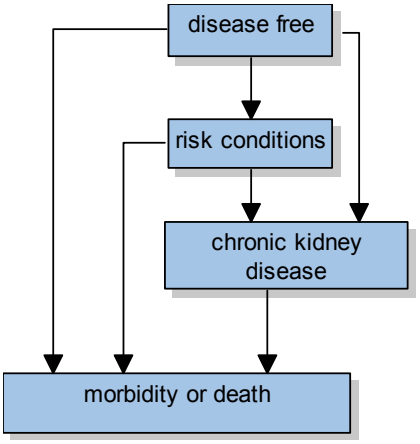


Figure 2-2 CKD transition module

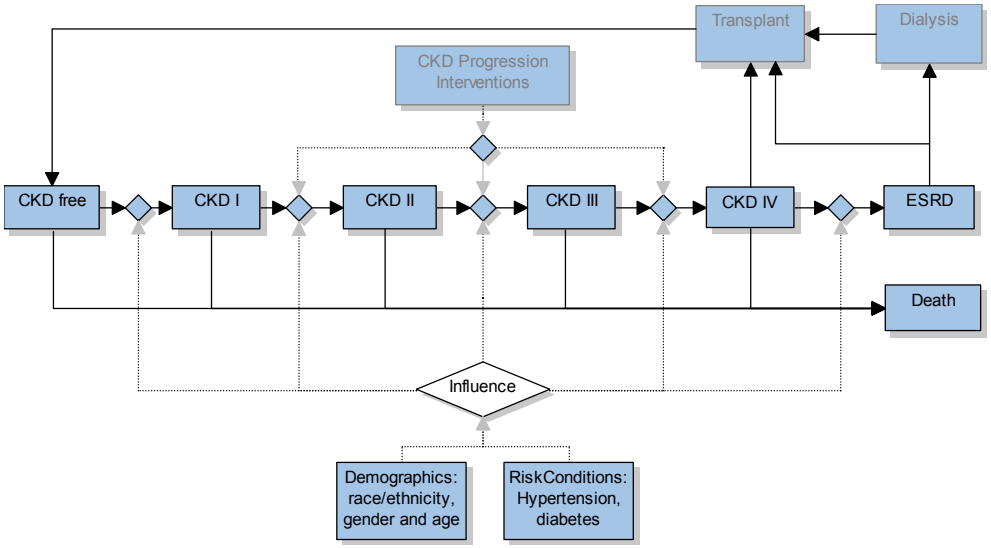


Figure 2-3 Risk condition module

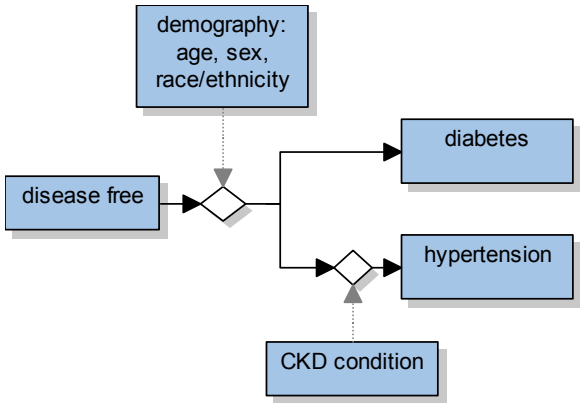


Figure 2-4 Model structure overview

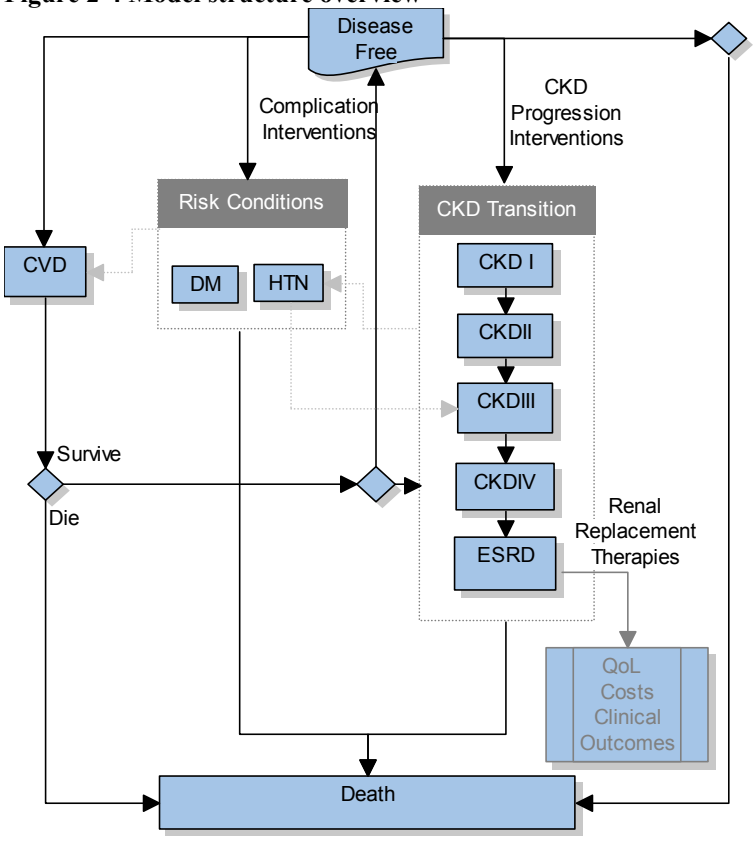


Table 2-1 CKD variable definition

CKD stage	
No CKD	GFR >= 60 without albuminuria
Stage 1	GFR >= 90 with albuminuria
Stage 2	GFR 60-89 with albuminuria
Stage 3	GFR 30-59
Stage 4	GFR 15-29
Stage 5	GFR < 15

Note: albuminuria is defined based on the gender of the respondent (Males: albumin-to-creatinine ratio >= 17 mg/g; Females: albumin-to-creatinine ratio >= 25 mg/g)

Table 2-2 Controlled hypertension incidence, per 1000 life year

Age	white female	White male	black female	black male	Hispanic female	hispanic male
18-44	2	3	5	4	3	3
45-64	5	7	10	9	5	6
65-79	7	12	14	16	5	10
80+	11	17	26	17	15	15

Table 2-3 Uncontrolled hypertension incidence, per 1000 life year

Age	White female	white male	black female	black male	hispanic female	hispanic male
18-44	1	1	2	2	0	1
45-64	3	3	8	6	3	4
65-79	8	7	19	13	10	9
80+	19	19	40	37	15	21

Table 2-4 Controlled diabetes incidence, per 1000 life year
diabetes controlled

Age	White female	white male	black female	black male	hispanic female	hispanic male
18-44	0.3	0.8	0.5	1.1	0.9	1.0
45-64	1.1	2.0	1.6	1.8	3.3	2.7
65-79	4.9	7.7	8.6	10.0	13.1	14.9
80+	19.7	31.2	30.9	57.4	68.3	71.7

Table 2-5 Uncontrolled diabetes incidence, per 1000 life year
diabetes uncontrolled

Age	white female	white male	black female	black male	hispanic female	hispanic male
18-44	0.6	0.6	1.6	1.9	2.3	2.6
45-64	2.0	3.0	6.1	8.2	8.3	10.5
65-79	7.1	11.5	20.9	28.7	30.4	34.4
80+	26.7	41.2	77.4	48.7	85.4	100.3

Table 2-6 Sample size and Data sources

CKD stage	N	Average Weight	Sources
Free	41,778	4,287	NHANES III
1	36,270	683	NHANES III
3	17,909	539	NHANES III
4	5,509	100	USRDS Incidence
5	5,372	75	USRDS Prevalence

Table 2-7 Distribution of the Initial Sample

		White female	White male	Black female	Black male	Hispanic female	Hispanic male	All Pop.
		38.6	36.6	6.1	4.9	7.1	6.8	100.0
CKD	CKD free	83.8	83.6	82.5	81.4	85.5	85.5	83.8
	CKD 1&2	9.2	11.8	13.2	14.7	11.9	13.3	11.1
	CKD 3	6.6	4.2	3.5	3.0	2.5	1.0	4.7
	CKD 4	0.2	0.3	0.4	0.4	0.0	0.0	0.2
	CKD 5	0.1	0.2	0.4	0.5	0.1	0.2	0.2
Hypertension	HTN free	69.6	72.1	59.0	67.9	74.8	75.8	70.6
	Controlled	18.2	18.6	24.2	19.3	16.4	15.4	18.4
	Uncontrolled	12.3	9.4	16.9	12.8	8.9	8.8	11.0
Diabetes	DM free	94.4	93.7	90.0	91.9	93.4	92.9	93.6
	controlled	2.3	2.3	2.9	1.8	2.0	2.3	2.3
	uncontrolled	3.3	4.1	7.2	6.3	4.6	4.9	4.2

Table 2-8 Comparison between model prediction and observed data, rate per thousand

	All		white male		white female		black male		black female	
Age Group	Obs	Model	Obs	Model	obs	model	obs	model	obs	model
35-39	1.6	2.3	1.9	1.6	2.9	2.5	2.2	2.2	3.7	3.5
40-44	2.4	3.3	2.8	3.0	4.3	4.0	3.3	4.1	5.5	5.6
45-49	3.6	3.9	4.2	3.8	6.8	9.1	5.1	5.0	8.8	9.7
50-54	5.2	6.2	6.0	6.3	9.7	10.1	7.0	7.2	13.0	17.9
55-59	8.0	9.5	9.4	8.1	13.7	11.8	9.9	9.5	18.5	18.1
60-64	12.6	11.2	14.8	16.6	19.5	20.6	14.9	22.9	25.7	23.0
65-69	19.3	18.9	23.3	22.9	26.6	25.8	21.4	27.2	33.7	32.8
70-74	29.7	31.3	36.3	37.9	39.8	34.4	32.9	34.3	49.6	57.3
75-79	45.6	45.4	55.2	55.6	58.0	64.2	49.4	53.9	71.4	73.6
80-84	74.0	73.5	89.6	93.9	85.2	89.3	75.6	59.7	102.5	99.2
85 and older	153.2	159.6	169.0	160.8	147.5	166.3	144.4	139.7	154.9	161.2

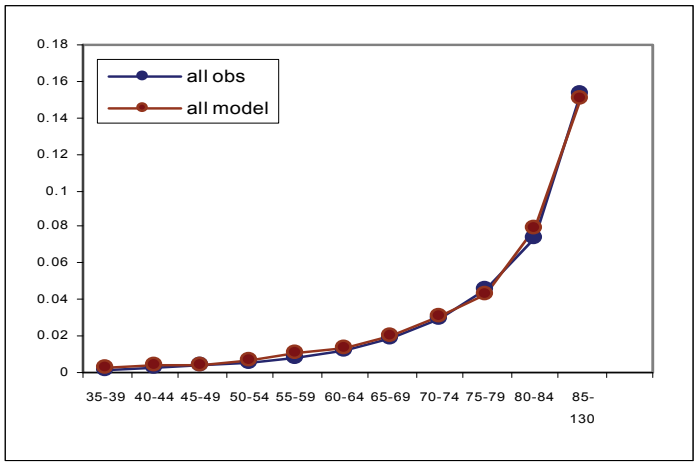
Note: observed data is obtained from National Vital Statistics Report 2000. www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf accessed on March 2009.

Table 2-9 Comparison of diabetes prevalence predictions

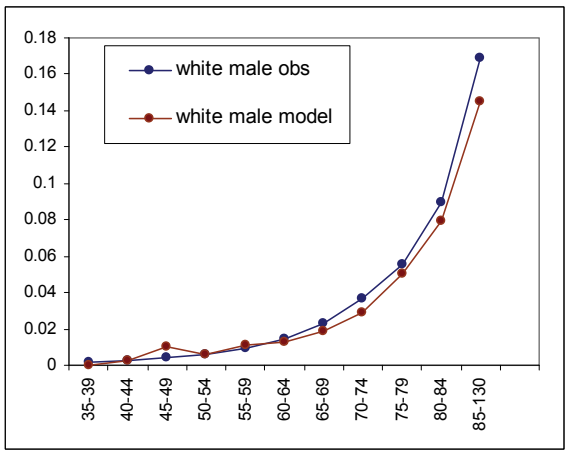
Year	45-64		65-74		75+	
	Honeycutt et al.	Model Predicted	Honeycutt et al.	Model Predicted	Honeycutt et al.	Model Predicted
2000	8.18	9.67	14.94	16.89	13.07	14.72
2005	9.09	9.94	16.98	17.80	14.54	14.94
2010	10.17	11.56	18.09	19.98	16.34	16.01
2015	11.33	12.13	18.78	20.03	17.99	18.13
2020	12.39	13.76	19.69	21.83	19.44	21.47

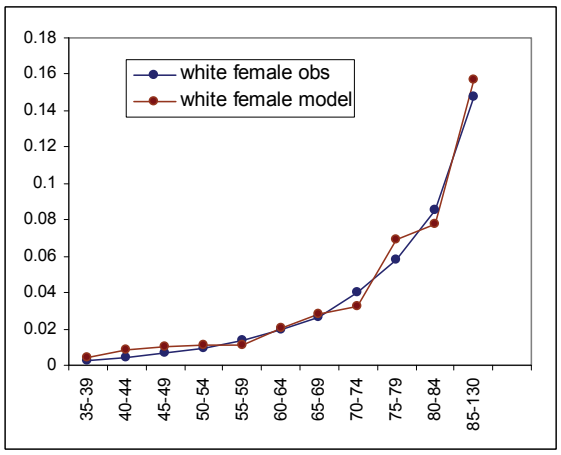
Note: Honeycutt et al. 2003.

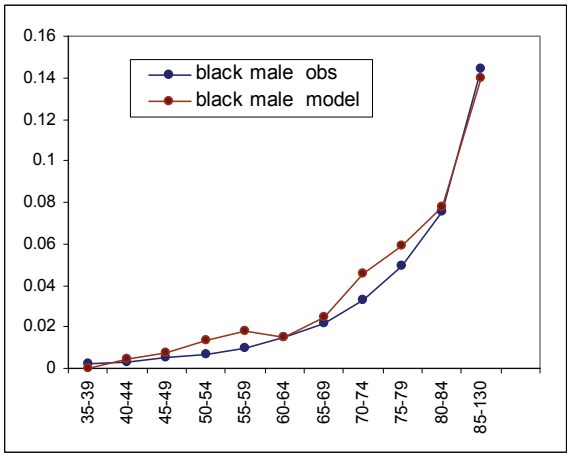
Figure 2-5 Mortality(2000)



Source: the observed mortality from National Vital Statistics Reports, United States Life Table, 2000. http://www.cdc.gov/nchs/data/nvsr/nvsr51/nvsr51_03.pdf







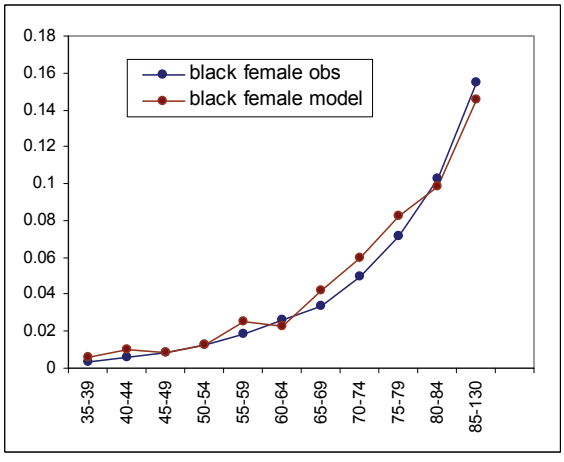
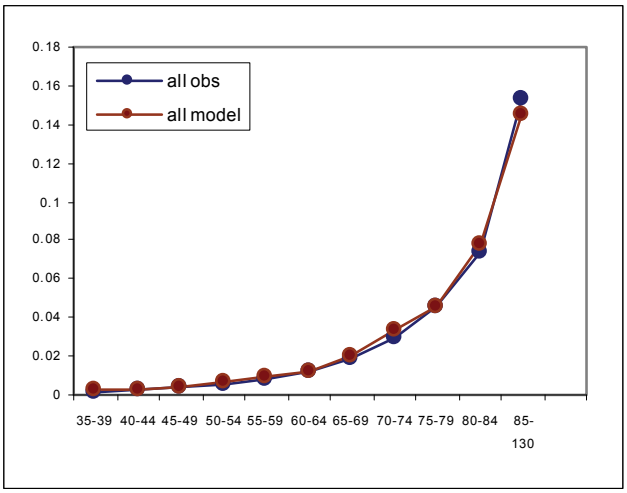
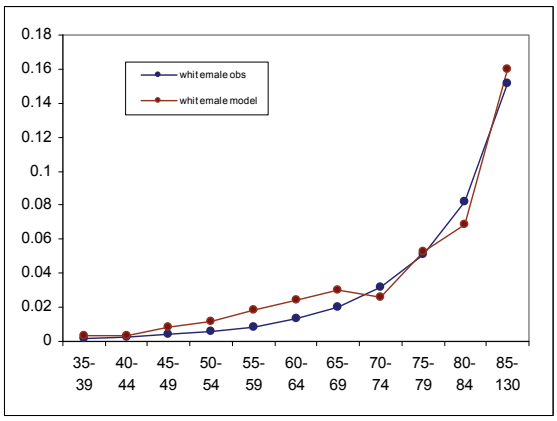
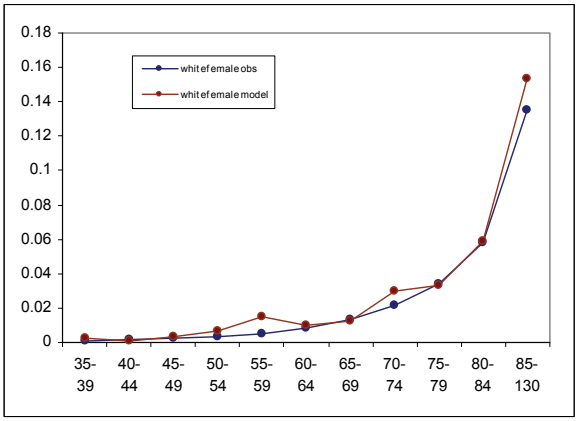
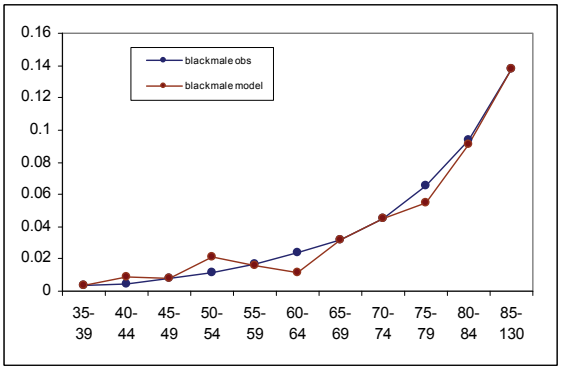


Figure 2-6 Mortality (2005)









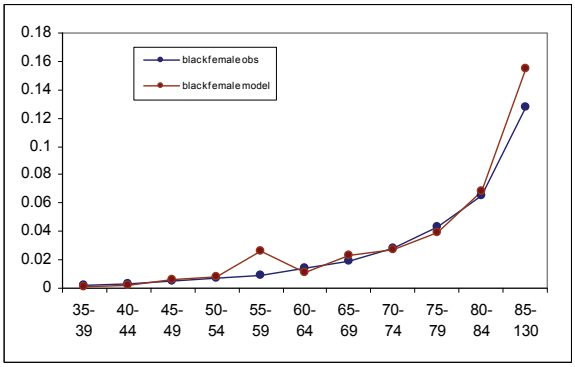


Figure 2-7 Hypertension (including controlled and uncontrolled) Prevalence

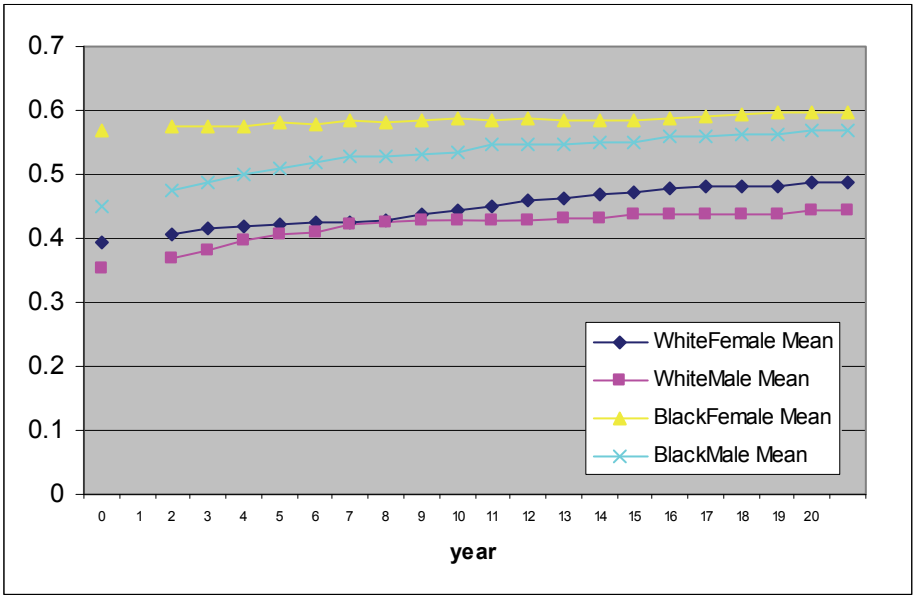


Figure 2-8 Controlled Hypertension Prevalence

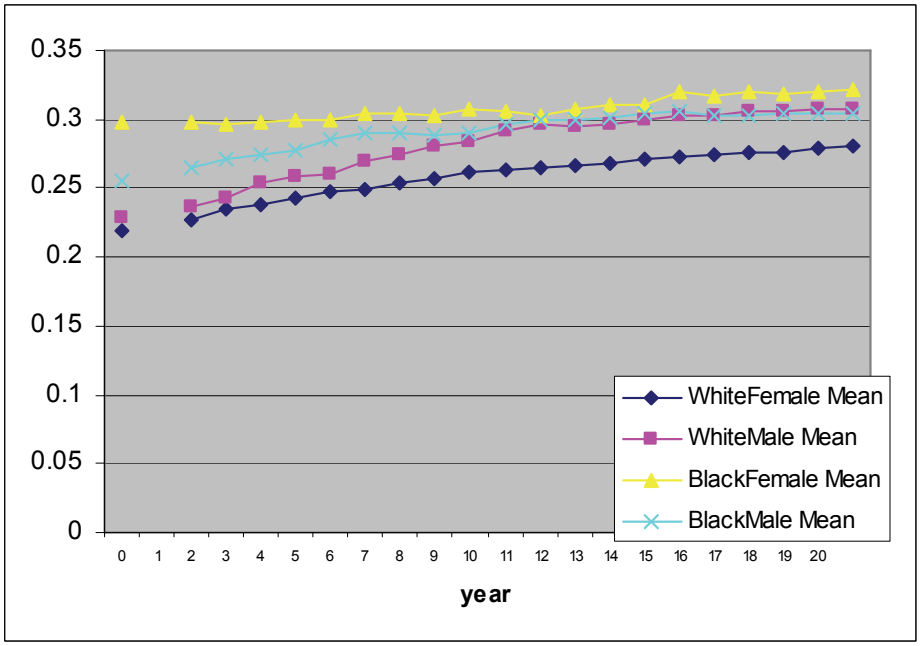


Figure 2-9 Uncontrolled Hypertension Prevalence

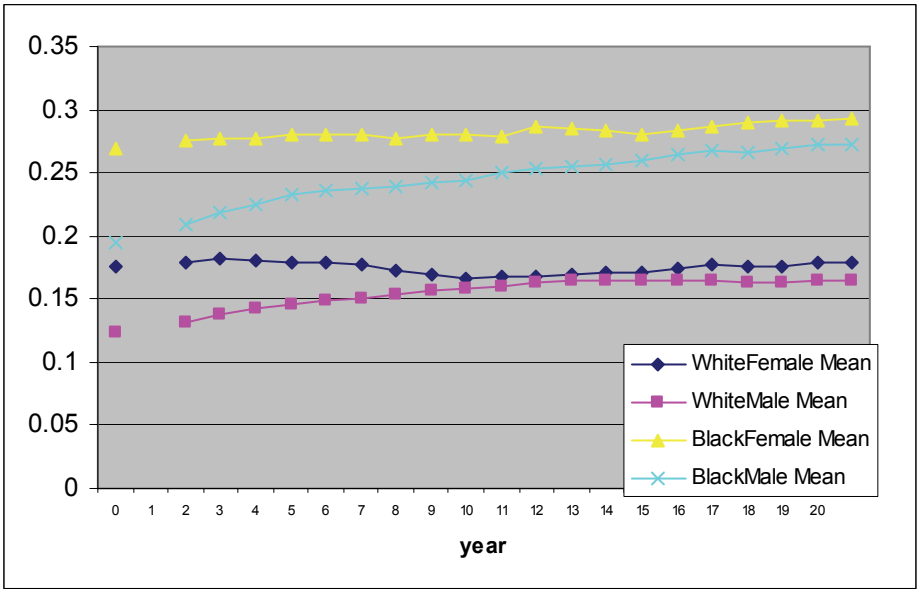


Figure 2-10 Diabetes (including controlled and uncontrolled) Prevalence

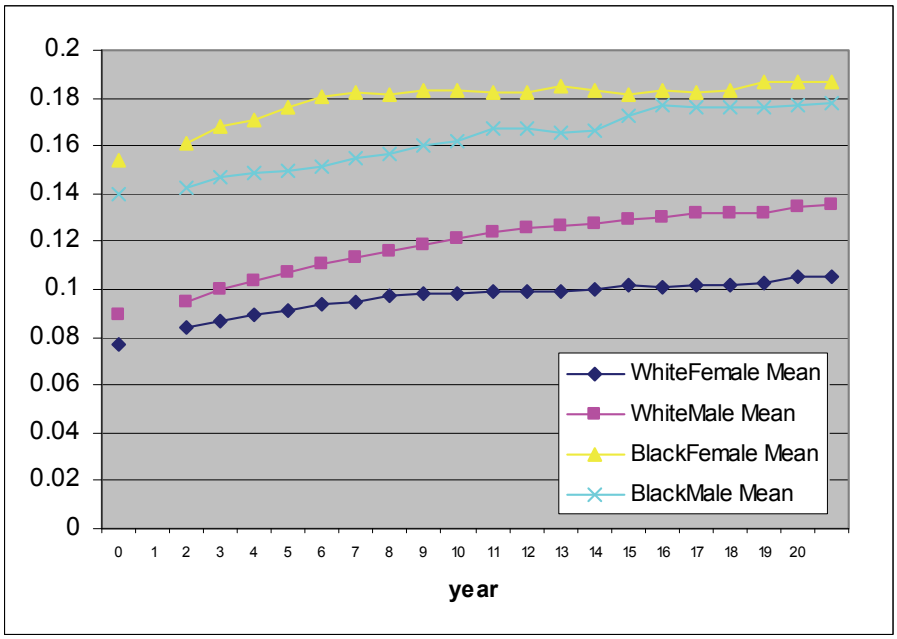


Figure 2-11 Controlled diabetes Prevalence

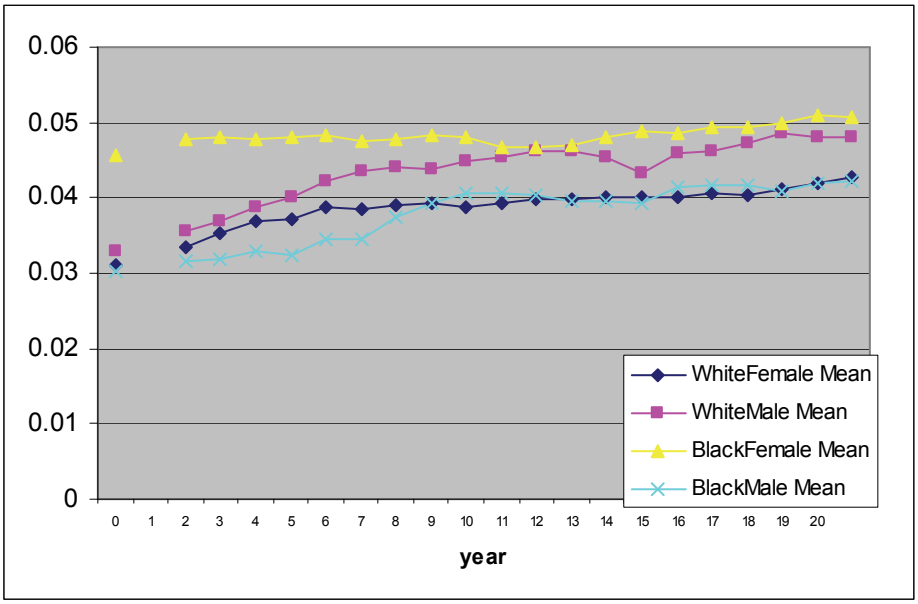


Figure 2-12 Uncontrolled diabetes Prevalence

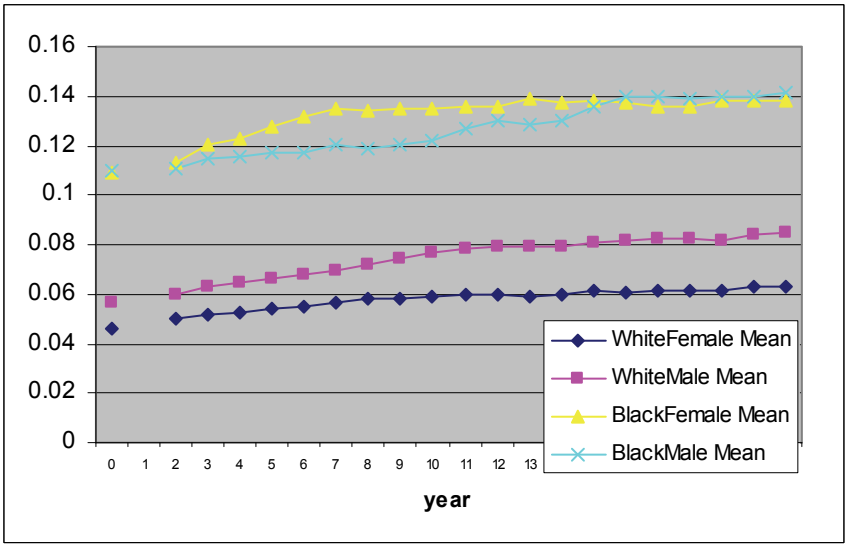


Figure 2-13 CKD (including all stages) Prevalence

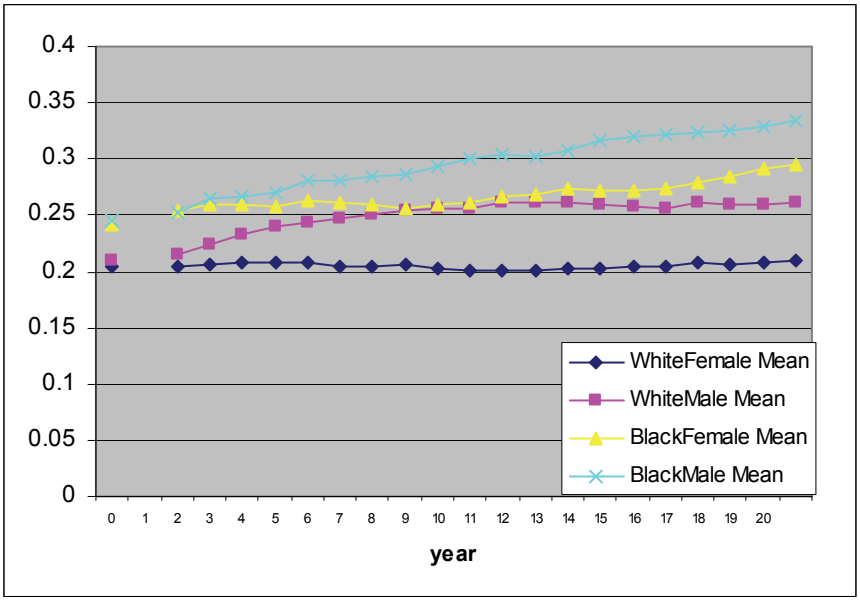


Figure 2-14 CKD Stage 1&2 Prevalence

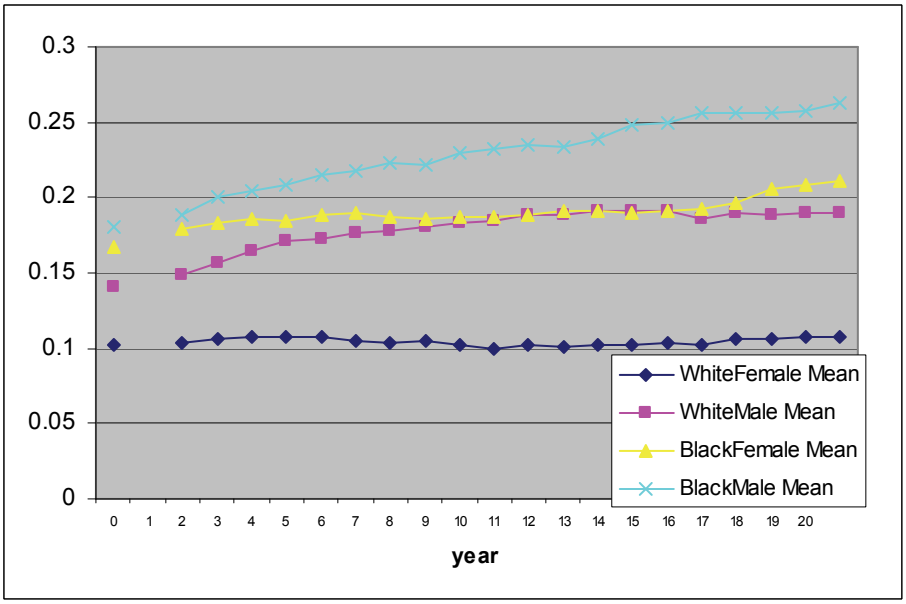


Figure 2-15 CKD Stage 3 Prevalence

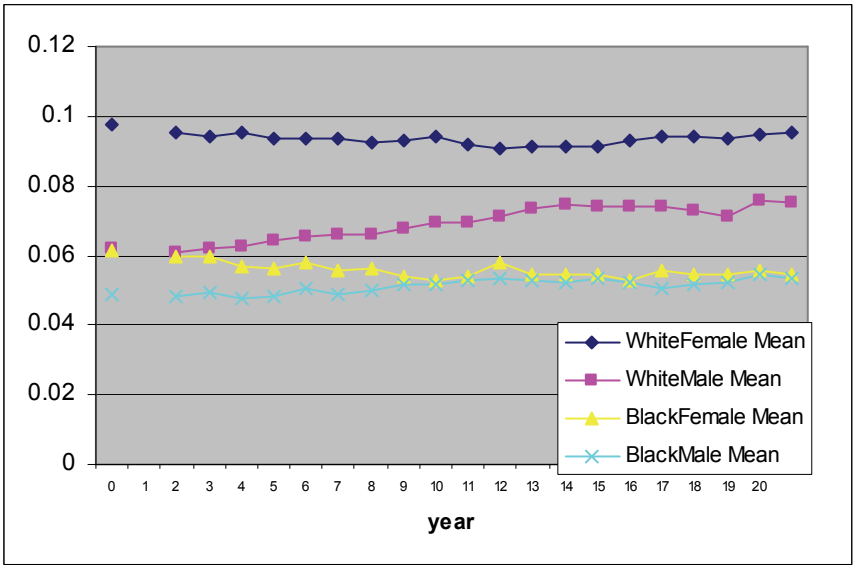


Figure 2-16 CKD Stage 4 Prevalence

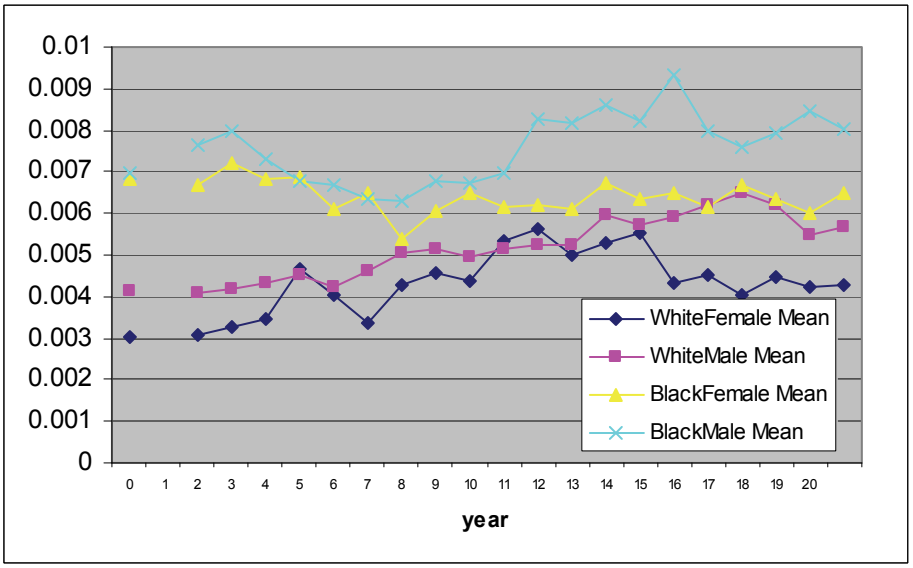
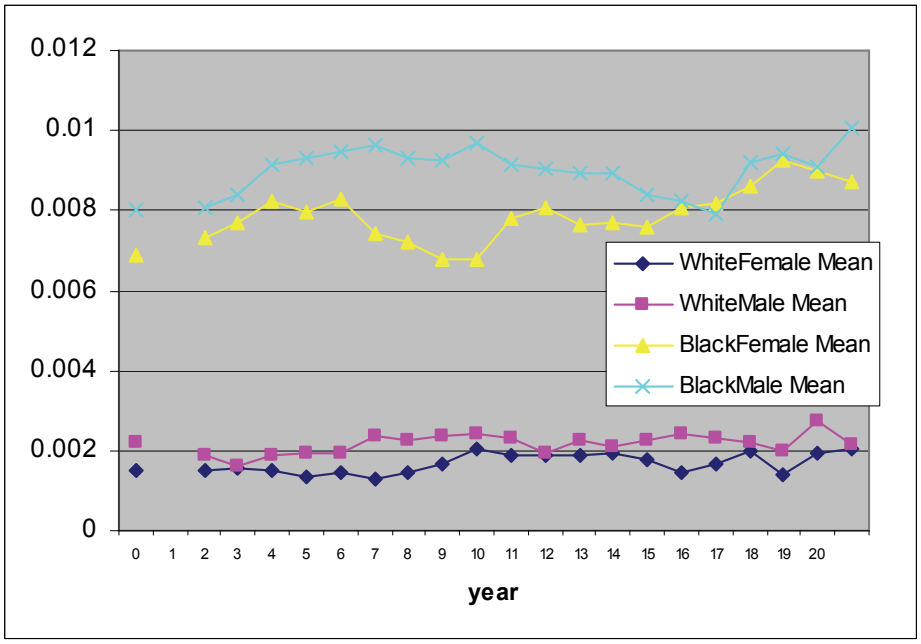


Figure 2-17 CKD Stage 5 Prevalence



Chapter 3 Hypertension Control and Chronic Kidney Disease Outcomes among US Adults

Abstract

Chronic Kidney Disease (CKD) is increasingly recognized as a public health concern in the United States. Hypertension is an important independent predictor of CKD development and progression. Despite the growing evidence that hypertension control reduces the risk of CKD, hypertension care is delivered inadequately and the adherence to established blood pressure targets is low. Using a CKD simulation model, we examined the impact of improving high blood pressure control on CKD outcomes at population level. The result shows the average quality-adjusted life years increases by 0.28 QALYs if we could reduce current uncontrolled hypertension and the new incidence by half. The 30 years medical cost saving due to the intervention is estimated to be $789 per person. The strategy both improves health outcomes of CKD and saves money. The cost savings on the ESRD associated health care is substantial, offsetting the investment on the upstream hypertension control. The results support that more public health efforts should be directed to improve the hypertension awareness and control as one effective early intervention strategy on CKD.

Introduction

One in eight Americans is now living with Chronic Kidney Disease (CKD) (Coresh, et al., 2007). Over the last decades, the number of CKD patients has risen progressively due to the growth of hypertension, diabetes, and the obese and elderly populations in the U.S. CKD leads to End Stage Renal Disease (ESRD), causes morbidity and premature mortality(Obrador, et al., 2002). Treating CKD imposes a large economic burden on patients, the health care system, and society.

High blood pressure is an important predictor of the development and progression of chronic kidney disease as well as morbidity and mortality in patients with CKD. It has been well established that hypertension control is the single most efficacious pharmacological intervention that prevents incidence and progression of the disease(Weir, 2005). However, high blood pressure control is being delivered inadequately in the U.S and adherence to the targeted blood pressure level is low(Snyder, et al., 2008). The failure to achieve blood pressure control in our population, especially CKD population, makes a substantial contribution to the development of chronic kidney disease and subsequent renal failure (Weir, 2005).

The paper aims to evaluate the impact of improving high blood pressure control on population level CKD outcomes. The hypertension control is not of doubtful value. Many cohort studies have demonstrated that blood pressure control is associated with the lower

risk of strokes, coronary heart disease, cerebrovascular disease and other cardiovascular diseases (1978; 1997; Lenfant, 1997). Evidences also suggest hypertension control reduces the risk of renal insufficiency. However, it is unclear how this preventive intervention reduces the downstream burden of End Stage Renal Disease or whether it saves life-time cost of CKD care from societal perspective. This study contributes to the literature by estimating the effects of hypertension control on chronic kidney disease and related outcomes.

In this analysis, we hypothetically reduced current uncontrolled hypertension and the new incidence and accessed the impact on the economic and health outcomes of CKD. We found the early intervention saved both lives and money. The average quality-adjusted life years increased by 0.28 QALYs if we reduced current uncontrolled hypertension and the new incidence by fifty percent. Over 30 years, the discounted medical cost decreased by $789 per person in the intervention scenario. The cost on early hypertension intervention were offset by the savings resulted from the downstream medical events prevented. The result suggests an early intervention on hypertension control can effectively relieve the burden of end-stage renal disease.

Background

CKD is increasingly recognized as a public health problem

The burden of chronic kidney disease is growing in the United States and worldwide. In 2002, the total number of Americans living with CKD was estimated to be 19.2 million, representing 11% of the adult US population; the 0.22% of the population estimated to have ESRD comes from the large group of individuals with early CKD (Coresh, et al., 2003). The future incidence of CKD and ESRD is expected to grow with aging of the population and the increasing prevalence of other chronic illness such as hypertension and diabetes. Projections to the year 2010 estimate an annual 4.1% increase in incident ESRD cases (Xue, et al., 2001). By 2030, it is estimated that the annual number of people with new onset of ESRD will exceed 450,000, and those receiving dialysis on who have had kidney transplants will exceed 2 million (Gilbertson D, 2003). The increasing prevalence of CKD is not unique to the US. Studies from Europe, Australia, and Asia confirm the high prevalence of CKD (Chadban, et al., 2003; Hillege HL, 2001; Iseki., 2003). The prevalence was estimated between 6% and 11%. CKD has become a global public health challenge (Bello, et al., 2005; El Nahas, 2005; Levey, et al., 2007).

CKD causes morbidity and premature mortality. The adverse outcomes of CKD include not only progression to kidney failure but also complications of reduced kidney function and increased (10 to 30 times) risk of cardiovascular disease (CVD)(O'Hare, et al., 2006). Patients with CKD are far more likely to die, principally from CVD, than to develop kidney failure (O'Hare, et al., 2006). Deaths caused by CKD were estimated at 71,000 in 2000 and are expected to increase to 352,000 in 2030(Gilbertson D, 2003). Recently the Centers for Disease Control and Prevention (CDC) listed kidney disease as the ninth leading cause of death in the United States (Mokdad, et al., 2005).

CKD poses a tremendous economic burden on the US society. Total health care expenditures on kidney failure exceeded $25 billion in 2002 and are estimated to be nearly $40 billion in 2010 (USRDS, 2004). As a comparison, the NIH budget during that year was $23 billion, which represents all of the NIH efforts for biomedical research in all fields. Because patients with kidney failure will be automatically covered by Medicare, nearly two thirds of the health care costs come from Medicare (USRDS, 2004). Although ESRD patients represent less than 1% of the Medicare population, their care consumes 6.4% of the health care expenditures by Medicare(USRDS, 2004). The direct and indirect income loss for patients is between two to four billion a year (USRDS, 2004). In addition, recent data indicates that the total health care resources used for CKD patients are 1.6 to 2.4 times those resources used by the ESRD population (Hunsicker, 2004). The large economic burden may finally give rise to studies focusing on effectiveness of preventive care for patients with CKD on a par with studies of patients with ESRD.

Hypertension control is clinically effective but inadequately applied

The large burden of CKD does not appear to be inevitable. There is evidence that earlier stages of CKD can be detected and treated and that adverse outcomes of CKD can be prevented or delayed (NationalKidneyFoundation, 2002). Unfortunately many patients with CKD still receive suboptimal care (McClellan, et al., 1997; Obrador, et al., 1999). The disease is not being detected early enough to initiate treatment regimens and reduce

death and disability (NationalKidneyFoundation, 2002). In addition, many interventions are being delivered too late to improve population-based outcomes (Levey, et al., 2007). It is estimated that CKD patients in the United States only receive a little over 50% of recommended care (Obrador, et al., 2002).Although not all progression to kidney failure is avoidable the 50-70% of patients whose first presentation of kidney disease is kidney failure suggest that there is a great need for early intervention program(Obrador, et al., 1999).

Control of hypertension is the single most efficacious pharmacological intervention that prevents the progression of renal insufficiency (Jafar, et al., 2003). CKD is either a cause or a consequence of hypertension, and its prevention and treatment are tied closely to the treatment of high blood pressure. Many cohort studies in the US have identified hypertension as a leading risk-increasing condition in the general population for the development of chronic kidney disease (Haroun, et al., 2003; Klag, et al., 1997). High blood pressure is also commonly linked to both renal and cardiovascular disease, which are the leading causes of death among CKD patients. For the hypertensive population, the relative risk of CKD progression ranges from 1.8 to 3.1 (Jafar, et al., 2003). High blood pressure also increases the chance of cardiovascular disease (CVD) by 3-6 times (D'Agostino, et al., 2008) and CVD mortality by 13 to 23 times (Gerstein, et al., 2001). Therefore blood pressure control has been advocated as a fundamental treatment to prevent and slow down the progression to advanced CKD. Evidence also suggested a benefit of reduction in cardiovascular disease events by tight hypertension control (Wald and Law, 2003). Early intervention on hypertension could influence both renal and

cardiovascular morbidity and mortality. There is significant evidence to support aggressive BP control in patients with CKD, and the current hypertension guidelines (Bakris, et al., 2000; Chobanian, et al., 2003) recommend a target BP value <130/90 mm Hg for these patients.

However, blood pressure control for CKD patient population is inadequately applied in current practice (Peralta, et al., 2005). Inadequate control of hypertension for the preponderance of hypertensive American has been repeatedly described(NationalCenterforHealthStatistics, 1996). It is estimated the adherence rates to hypertension control guidelines is between 25% and 45% (the targets levels are <140/90 mm Hg) (Borzecki, et al., 2003; Hicks, et al., 2004; Hyman and Pavlik, 2001). Similar levels of inadequate blood pressure control were observed for patients with overt CKD(Peralta, et al., 2005). Among hypertensive individuals with an elevated serum creatinine level, twenty seven percent and eleven percent had blood pressure <140/90 and 130/85 in NHANES III, respectively(Coresh, et al., 2001). Comparing to the patients in advanced stages, CKD patients in the early stages were 40 percent less likely to be aware of their hypertensive status. Comparing to non-CKD patients, they are 43 percent less likely to be treated for their hypertension (Snyder, et al., 2008). Less than one third of identified CKD patients get an Angiotensin-Coverting Enzyme (ACE) inhibitor which has been widely advocated as blood pressure management tool for the patients with CKD (McClellan, et al., 1997). Barriers to hypertension care and control are remarkably persistent and continue to impede improvement in rates of awareness, treatment, and control.

The gap suggests a great potential for decreasing renal disease incidence and related mortality by optimizing blood pressure treatment in this high-risk population. This strategy may save money by deferring the extremely high costs of kidney failure, but the primary beneficial outcome will be better health, and a shift in the workload for the health services to more upstream treatments. From a policy point of view, it is important to understand the magnitude of the impact and how much it will cost at population level. The paper addresses this question by assessing the health and economic outcome of CKD care in a "what if" scenario where the hypertension control is improved significantly.

Literature

Hypertension has a strong and causative association with CKD. Hypertension forms part of the pathological mechanism by which CKD is initiated, and is also a consequence of reduced kidney function. The kidneys regulate blood pressure by varying the amount of sodium and water excreted to maintain a homeostatic level. As CKD evolves, the kidneys' capacity to maintain blood pressure homeostasis declines progressively. For this reason in almost all cases of CKD, rising blood pressure occurs concomitantly with progressive decline in kidney function. At the same time, hypertension and CKD promote arteriosclerosis, potentially leading to aggravation of the underlying kidney disease at the level of large (renal artery stenosis) and small vessels (hypertensive nephrosclerosis). Population studies have shown that progressive increases in blood pressure are associated with progressive increases in risk of ESRD (Cushman, 2003). Data from the Multiple

Risk Factor Intervention (MRFIT) cohort indicate mild elevations in blood pressure (SBP 140-159, DBP 90-99 mm Hg) are associated with a 3-fold increase in the risk of developing ESRD after adjustment for other risk factors(Klag, et al., 1996). Severe hypertension (SBP 180-209, DBP 110-119 mm Hg) was associated with an 11-fold increase in risk, and very severe hypertension (SBP >210, DBP >120 mm Hg) with a 22-fold increased risk. Elevated blood sugar levels in diabetes, if uncontrolled, can lead to microvascular damage as well as kidney damage. Chronic hyperglycaemia and the associated disturbances of carbohydrate, fat and protein metabolism cause permanent damage to kidneys (Ritz and Orth, 1999).

Several studies had been conducted aiming to evaluate the effect of antihypertensive medicines (mainly Angiotensin-Converting-Enzyme or ACE Inhibitor) on CKD outcome. Using clinical data obtained from a 3-year randomized clinical trial [the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency (AIPRI) study], Hogan et al. (2002) developed a four-state Markov model to evaluate the effectiveness of benazepril on slowing the CKD progression. In the clinical studies on which this economic analysis was based, patients with chronic renal insufficiency of various etiologies were randomized to antihypertensive therapy with or without concomitant benazepril. Over 7 years of analysis, patients randomized to antihypertensive treatment with concomitant benazepril therapy incurred on average USD12991 (1999 values) lower medical costs than patients prescribed antihypertensive treatment without benazepril, and obtained an additional 0.091 quality-adjusted life years (QALYs). Costs and QALYs were greater for the benazepril arm than the placebo arm for all years of analysis.

Benazepril therapy as a component of antihypertensive treatment of persons with chronic renal insufficiency initially costs money, but investment costs are recouped quickly and return on investment continues to grow (Hogan, et al., 2002). Similarly Hendry et al. developed an economic model to analyze the cost impact of ACE inhibitor treatment on progression to ESRD in diabetic patients over 4 years. Two scenarios were compared: one describing the progression of a cohort of 1000 patients receiving 25 mg captopril three times daily, and the other for an equivalent cohort without such prophylactic treatment. Previously published data were used to estimate the transition rates for each stage from the onset of renal failure until death. The discounted cost saving of ACE inhibitor treatment for a cohort of 1000 patients was estimated as 0.95 million pounds over 4 years. Prophylactic treatment with ACE inhibitors was predicted to provide substantial increases in life expectancy and reduction in the incidence of ESRD, while also providing significant economic savings (Hendry, et al., 1997).

These studies were specifically designed to evaluate the effectiveness of one particular medication using clinical trial data. To this end, they concentrated on one or two pharmacological interventions on current CKD patients. Based on the existing studies, it is not clear how CKD outcomes will be affected if hypertension is better controlled in general population, especially in long-term. It is also not clear that whether the early interventions on CKD risk conditions save life-time treatment costs since it essentially shifts work load to upstream health care on a larger population.

Scenario

A better control of hypertension prevents CKD and its comorbidities. In our analysis, we modeled the effects of hypertension control in the following ways: 1) better blood pressure control slows the decline of kidney function, and consequently reduces the risk of CKD incidence and prevents the disease progression. It prolongs the dwelling time of early stage chronic kidney disease, deferring ESRD and the need of dialysis and transplant; 2) with longer survival, CKD patients might develop more other complications; 3) it will also defer the occurrence of CVD events due to CKD and the related mortality. Such an intervention increases early treatments in two ways -- more people remain in early stage kidney disease and a higher percentage of them get treated.

In the hypothetical scenario, we assumed 50 percent of the current uncontrolled hypertensive patients who also had stage 1, 2 and 3 CKD switched to controlled cases. Additionally, we reduced the annual incidence of uncontrolled hypertension by 50 percent by some long-term improved controlling strategies – these people become incident controlled hypertension cases. It is practically feasible to achieve a fifty percent of risk reduction though appropriate interventions (1990). For simplification, we also assumed the switchers are a random sample of the population, so the cost and benefit of the switch is proportional to the percent of change and the incremental cost-effectiveness ratio will be independent of the percent of people that switch.

The hypertension variable is defined by two variables measured in NHANES: 1) whether subjects were diagnosed with hypertension; and 2) the onsite measurement of systolic and diastolic blood pressures. Individuals are hypertension free if they reported never being told they were hypertensive. In the current model, we did not model the diagnosis or screening of risk condition so we ignore the undiagnosed cases of hypertension and diabetes in NHANES III (about 30% of hypertensive patients were unaware of their condition(Hodgson and Cai, 2001)). Individual has controlled hypertension if she was diagnosed as hypertensive and the systolic blood pressure is lower than 140 and diastolic blood pressure is lower than 90. An individual has uncontrolled hypertension if she was diagnosed as hypertensive and the systolic blood pressure is higher than 140 or diastolic blood pressure is higher than 90. While hypertension is assumed a chronic and incurable condition in the model, it can be controlled by appropriate treatment. With good control, the adverse effect of hypertension on CKD can be significantly reduced.

We assume patients can lower their blood pressure to targeted controlled level through routine hypertension care. The routine care includes antihypertensive medication therapy, counseling on diet and behavior changes. Examples of outcomes studies demonstrating the impact of antihypertensive drug therapy include "a vigorous stepped care approach when patients do not reach target blood pressure levels" that significantly improved the hypertension outcome(Fahey, et al., 2006). It was demonstrated that the appropriate use of antihypertensive agents can reduce the blood pressure by 10-13 percent(Long, et al., 2006). Non-pharmacologic means have also been shown effective in preventing and delaying the onset of hypertension. Such advocated interventions include self-monitoring,

educational interventions directed to the patients, health professional (nurse or pharmacist) led care, organizational interventions that aimed to improve the delivery of care and appointment reminder systems (Fahey, et al., 2006). In the Trials of Hypertension Prevention (THP), it was found that a 3-year program of group meetings and individual counseling focused on dietary change, physical activity, and social support reduced the incidence of hypertension among middle-aged participants. The risk ratio for developing hypertension after 6 months was 0.58 relative to usual care(1990; Association, 2002). These efforts aim to provide the rationale or motivation for the behavior, such as knowledge, beliefs, values, and attitudes, or allow a predisposition to be translated into a behavior, for example, by facilitating the accessibility of health care resources and the acquisition of appropriate skills.

In the scenario, we also hypothesize certain health outreach efforts are needed to recruit new patients and initiate more hypertension care among the population. Effective hypertension control programs require a comprehensive approach that incorporates social, psychological, behavioral, economic, and biomedical components. Health outreach, which is a proven strategy, encompasses many of these approaches. It has been carried out at national, state, community and clinic levels(Welch and Hill, 2002). Community outreach varies from work-site hypertension programs, faith-based organizations, fire station fairs to pharmacists. Through direct education, onsite screening and treatment, and other valuable health demonstrations, the health outreach has been shown increases the awareness of hypertension condition, initiates treatments and enhances the treatment compliance(Welch and Hill, 2002).

Methods

To quantify the impact of the prevention strategy, we developed an analytical model to simulate the natural history of chronic kidney disease and its complications and treatment effect. The CKD model is a micro-simulation model to forecast the incidence, cost and health outcomes of CKD for the U.S. adult population. The model predicts the changes of health states in each individual's life history over the next 20 years. During this period, people can maintain their health, develop CKD, its comorbidities, and its risk-increasing conditions, or die. The model is based on the assumption that the natural history of chronic kidney disease and its complications and comorbidities can be described by a series of discrete health states that represents the progression of kidney function decline.

Within the general conceptual model we distinguish 3 sub-models describing the changes in three major dimensions of health states of interest: a module for the course of renal function decline from CKD free through stage 5 (End Stage Renal Disease), a module for the incidence and prevalence of CKD risk-increasing conditions (hypertension and diabetes), and the module for death and the incidence of Cardiovascular Disease (CVD), which accounts for more than 60 percent of CKD death.

In the model, a large number of people are followed as a cohort. The nationally representative sample was obtained from the National Health and Nutrition Examination Survey (NHANES III) and the United States Renal Disease System (USRDS). Within

the model, CKD progress from CKD free to End Stage Renal Disease (ESRD) with the presence of albuminurea and the decline of estimated Glomerular Filtration Rate (eGFR). Treatment, high blood pressure, diabetes and demography influence the probability of the disease progressing to higher stages. In advanced stages (stage 4 and 5), dialysis and transplant are additional influencing factors on disease progression and health care costs, and transplantation can lead to recovery from ESRD. The incidence of hypertension is also affected by CKD, but diabetes is assumed independent of CKD. Individual can experience either one condition or have both risk conditions. The chronic conditions are persistent and incurable in the model but can be controlled through treatment. The appropriate control reduces their impact on CKD progression and Cardiovascular Disease (CVD). We collected the health utilities and costs information annually and then compared them in status quo and in intervention. For more details on the model, see Chapter 2 in the dissertation.

Costs

We assume current routine hypertension control therapy will achieve the target of risk reduction. The routine care includes prescription drug, inpatient and outpatient care, office visit and home-based care etc(Balu and Thomas, 2006). The medical cost of the routine hypertension care was obtained from the published literature. According to Balu et al's estimate from Medical Expenditure Panel Survey(MEPS), the total incremental annual direct expenditures for treating diagnosed hypertensive patients is $1,509 (2008 value)(Balu and Thomas, 2006). Table 1 presents the cost estimates from their study.

Mean incremental prescription medicine expenditure, inpatient visit expenditure, and outpatient visit expenditure by hypertension patients was estimated to be $US 730, $458, and $153 respectively. These three categories constituted over 90% of the overall incremental expenditure for treating hypertension. We also compare other costing analyses of hypertension treatment. They indicate similar levels of annual medical cost of hypertension treatment (French, et al., 2005; Hodgson and Cai, 2001). Therefore we use Balu et al's estimate and assume it costs $1,509 annually to switch an uncontrolled hypertension case to a controlled hypertension case. It should be noted that the hypertension was not distinguished by controlled or uncontrolled in their study. If we assumed that the control was obtained through the preventive measures in the hypertension prevention trial then these costs, particularly inpatient, and emergency care visits may be less. Therefore they may overestimate the cost of treating uncontrolled hypertension. On the other hand, if treating uncontrolled hypertension cost more than controlled hypertension, their results may underestimate the cost of switching uncontrolled hypertension to controlled hypertension. To this end, we varied the cost widely in our sensitivity analysis. The cumulative present costs assume future costs are discounted at 3% a year.

We also assume a cost of recruiting new patient to initiate the treatment. This could include the cost of screening at clinical settings, educational projects, or health fairs in community or other health outreaches. The cost of screening for blood pressure in a clinician's office as part of a routine physical examination is minimal. Public approaches have used mechanisms ranging from national educational campaigns, work-site health

promoting programs to community-based outreach projects. These costs vary depending on the types, frequency and the level of the programs(Welch and Hill, 2002). For example, Brosnan et al estimated that it takes $28 per person to screen hypertension and overweight using a community partnership model (Brosnan, et al., 2008), while Silverberg et al found the average cost of $2-3 if using shopping centers to screen hypertension (Silverberg, et al., 1974). Assuming 10 to 15 percent of the screened eventually get treated (Borzecki, et al., 2003), the cost of recruiting a new patient could be at least ten times higher than that average cost. We therefore varied the cost substantially in our sensitivity analysis, with the cost ranging from zero to $1000 per person.

Certain fraction of the current hypertensive population has been under routine hypertension care. They have lower risk of uncontrolled hypertension and the effect has been taken into account in the incidence parameters used in the model. In other words, our parameters already reflect the fact that some patients are under routine therapy in the status quo. For that reason, we did not consider the cost associated with it as part of the incremental intervention cost.

The direct medical cost of CKD treatment is obtained from an evaluation by Hogan et al (Hogan, et al., 2002). The costs were reported by CKD stages. In their estimates, costs of dialysis, renal transplantation and post-transplant maintenance care were obtained from the United States Renal Data System (USRDS), and the estimates of direct medical costs in the 6 months preceding death were derived from the Healthcare Financing

Administration (Hogan, et al., 2002). In addition to these annual costs, we will add in event costs for cardiovascular disease event, for transplant, and for initial and continuing costs of dialysis. The medical cost of cardiovascular disease event is obtained from Hodgson and Cohen(Hodgson and Cai, 2001). For people without any conditions listed in the model, we assume same level of medical cost in status quo and intervention scenario, therefore they will not affect comparisons of kidney disease interventions when we calculate the incremental cost. However, to account for the total living costs that may accrue as a result of the implementation of life-prolonging interventions, we assume a $20,000 for every additional year people live after intervention in the sensitivity analysis, as recommended by Meltzer (Meltzer, 1997; 2001). All the costs were updated to 2008 dollar values using the Medical Component of the Consumer Price Index[14] .

Table 1 summarizes direct medical costs of CKD treatment, annual medical cost of diabetes, and the costs of adverse health events including CVD, transplant, dialysis and death. All the costs are discounted by 3% annually. Because of considerable uncertainty about cost estimates, we varied these parameters widely in sensitivity analyses.

Utilities

Health utilities measure the decline in health related quality of life due to functional limitations and discomfort. Health utility scores range from zero to one, where zero represents death and one represents perfect health. They are affected by age and disease.

[14] http://data.bls.gov/PDQ/servlet/SurveyOutputServlet;jsessionid=f030ff574792$3F$3F$1 [Accessed 2009 March 10]

Health utilities employed in the model were determined by analytical estimates based on reference to the quality-of-life literature (Anis, et al., 2006; Boulware, et al., 2003; Brown, et al., 2000; Hogan, et al., 2002). The progression of disease results in a decrease in the health utility scores. Health utility scores for ESRD were further adjusted by the status of transplantation. Quality adjusted life years (QALYs) are calculated by multiplying the utilities of various health states and the lengths of time individuals spend in them.

As our core interest, we model only chronic kidney disease and the major risk conditions and complications. For individuals with none of the conditions listed in the model, we assume an average health utility score which was estimated by Fryback et al. on Americans over 34. Because the model starts with ages 18 and over, we put in a somewhat higher value of health for people 18-34. Because young people have so few events, this value has a negligible effect on the results. We used the health utility scores measured based on EuroQol EQ-5D (EQ-5D) as recommended in their paper (Fryback, et al., 2007). The scoring algorithm was derived from time tradeoff assessment of health states made by a US population sample. This is one of the most widely used health status measure. Consistent with the literature, for subjects with multiple conditions, the utilities for the associated conditions were multiplied together. This assumes that diabetes, for example, reduces a subject's quality of life by the same percentage regardless of whether CKD also is present. However we made one exception for individuals in CKD stage 4 and 5 and individuals experiences CVD event. We did not multiply the CKD or CVD utility score with hypertension utility score because almost all of them had high blood

pressure (more than 80 percent of CKD stage 4 and 5 had hypertension in NHANESIII, for example) and hypertension is already taken into account when the utility scores were estimated.

The utility weights of hypertension were obtained from multiple sources (Anis, et al., 2006; Brunenberg, et al., 2007; Nagata-Kobayashi, et al., 2005). With no treatment, hypertension itself has little effect of current health utility, especially for younger age group. Therefore we assigned the same health utility score of general population from Fryback et al (Fryback, et al., 2007). Because hypertension is essentially asymptomatic and the side effects of treatment usually reduce utility, the utilities of treated hypertensive patients are generally lower than the ones of the untreated. We used the difference of treated and untreated hypertension utilities, which was estimated by Anis et al (Anis, et al., 2006), and applied it uniformly to all age groups. Table 2 presents the utility scores and sensitivity range employed in the model. The QALYs are discounted at a rate of 3% per year.

Result

To test the validity of the model result, we applied the model predictions against the observed national health statistics. We found that the prediction of age-specific mortalities over 2005 among the population age 38 and older is comparable to the estimates of CDC. Table 3 illustrates the observed and predicted mortality by age groups for overall population and white and black populations. The mortality rates of overall

population are virtually indistinguishable. The matches for both white and black populations are close. The predictions in Caucasian population are slightly better. The predictions in African American population have greater random variationd due to the smaller sample size. Please see Chapter 2 for more details of the model validation.

The prevalence of hypertension among the 38 or older American is predicted to increase from 25 percent to 37 percents over the 30 years, assuming treatment pattern is unchanged during the period of time. Without any intervention, the prevalence of uncontrolled hypertension increases from 9 percent to 13 percent. The figures 1-5 demonstrate the model projections under two different scenarios. The dotted lines show the prevalence patterns in the status quo. The solid lines show the prevalence under the hypothetical scenario. We do not assume any changes in incidence of hypertension overall, but the 50% increase in control leads to a reduction in the incidence of uncontrolled hypertension, and the prevalence of uncontrolled hypertension drops from 9 percent to 5 percent over the simulated 30 years while the numbers of controlled hypertensive patient increase. The improvement in hypertension controlled impacts the epidemic of CKD and the impact is more significant in the later years. A single intervention on hypertension control does not change the increasing trend of CKD prevalence; however it does reduce the numbers of all stage CKD patients, especially advanced stage CKD patients, among the US adult population over the next 30 years.

Base-case Analysis

Both health and economic outcomes of CKD care is improved with the reduction of adverse events of ESRD, dialysis initiation, renal transplant, cardiovascular diseases and death. By different time horizon, Table 3 shows how many adverse health events were reduced due to the intervention. Comparing to the status quo, 224 thousands ESRD case is reduced over 30 years because of the better control of hypertension among the population. Consequently the incident cases of dialysis and renal transplant dropped in the intervention scenario. Our model predicts the dialysis and transplant event drops by 368 thousand person-years and 56.7 thousand respectively. Additionally there are 248 thousand less cardiovascular disease events and 59 thousand less death in the intervention scenario over 30 years. And the cumulative benefits are greater with a longer time horizon. In table 4, we calculated the cost-saving due to the reduction of CKD-related adverse events. Overall, 58 billion dollars could be saved due to the improvement of hypertension control over 30 years. The reduction of dialysis and cardiovascular disease events is the major contributor to the cost-saving. The details can be found in table 3 and table 4.

The intervention is found cost saving with 30 years time horizon. In status quo, the total discounted quality-adjusted life years is 15.07 QALYs per person (20.6 for perfectly healthy one). The average QALY is 13.25 and 16.76 for people who had CKD and no CKD respectively. In the hypothetical scenario, the discounted quality-adjusted life year is 15.35 QALYs (13.61 QALYs for CKD patient and 16.97 QALYs for the others). The average QALY is improved by 0.28 (among the population who ever had CKD, the incremental QALY is 0.36). While the health outcomes are improved with the

intervention, the 30 year medical cost is found less than the one in status quo. On average, the medical cost was reduced by $789 per person. The result indicates a dominant strategy, meaning a better hypertension control saved both lives and money. Table 5 summarizes the base-case result of the cost and effectiveness in 30 years horizon. Improving hypertension control saves not only lives but also lifetime medical cost. The saving is largely due to the substantial saving from the downstream CKD care.

The cost-effectiveness of the intervention varies by the analytical time horizon. We expect to spend more initially, but the investment cost recoups gradually and the return continues to grow over time. In a shorter time period, the cost-saving is not enough to offset the extra spending on hypertension care, although the health is improved and more lives are saved. Table 6 indicates a highest incremental cost in 10 years and it declines over time. The incremental CE ratio hence decreases from $27,472/QALY to $2,507/QALY while we used from 10 years to 25 years as the time horizon. When the time horizon is over 30 years, the early intervention cost was entirely offset by the saving due to the adverse health events reduced. Better adherence to targeted blood pressure level slows the progression of renal insufficiency, hence prolongs the dwelling time in early stage CKD. Additionally the intervention improves health and reduces the mortality. Both of them will lead to more medical resources on early phase. Because patients would stay in early stage longer, a short time period does not allow the model to pick up the cost-saving due to the lower incidence of ESRD and its complications.

Sensitivity Analysis

We conduct an extensive 1-way sensitivity analyses by varying the values of health utilities and costs. The base-case result is robust to variation of all the inputs. Figure 6 and 7 illustrate the difference from base-case cost saving and QALY increase for each cost and utility parameter. We found that changing the cost of hypertension treatment, additional living cost, and dialysis treatment cost are most influential to the cost saving estimate, however none of the variations changes our base-case conclusion. As to the QALY, the utility of untreated hypertension is the most influential parameter (Figure 8). The second influential parameter is the living cost of the additional year due to the intervention but the effect is not considerable either, mainly because the prolonged unadjusted life year is relatively small. The effect of adding the cost of recruiting patients to start the hypertension care is minimal. The cost saving reduces from $789 to $525 when the cost was assumed to be $1,000 per treated patient. In summary, adjusting the value of these parameters within range does not significantly change the results. Furthermore, we repeated our analysis by changing the value of relative risk of CKD for hypertensive patients. The conclusion holds as long as the relative risk increase from hypertension is at least 63% of base-case estimates.

Medicare, as the major payer for the healthcare of elderly and ESRD population, would benefit from the early intervention with considerable saving. We calculated the medical costs incurred by the patients who are age 65 or older and the patients who experienced dialysis or renal transplant. We assumed 2/3 of the cost of kidney failure care is paid by Medicare(USRDS, 2004). It was estimated that the hypertension control saves Medicare

program $23 billion dollars on kidney failure care and $13 billion on cardiovascular diseases care over the 30 years.

In summary, the early intervention on hypertension control saved both lives (0.28 QALY) and money ($789.6). The cost savings were attributable to reduction in ESRD associated healthcare expenditures, most notably the cost related to subsequent dialysis. As such, our results strongly support the hypothesis that early intervention on hypertension is a cost-effective strategy to control chronic kidney disease.

Discussion

Although hypertensive patients are at high risk for chronic kidney disease and there is evidence that blood pressure control attenuates the rate of GFR decline and reduces the rate cardiovascular complications, adequate control remains suboptimal. This cost-effectiveness analysis of hypothetical hypertension control improvement demonstrates that compared with the status quo, the prevention would improve health and save the life-time healthcare cost from the societal perspective. The magnitude of observed changes in health outcomes is large and substantial as predicted in our model. These gains are achieved by moderate annual spending on hypertension control. The upstream costs are offset by the downstream expenditures saving due to the reduction of incidence of ESRD hence less transplant, dialysis and death. Within a shorter horizon, although the analysis does not indicate that the hypothetical intervention is cost saving, the incremental cost-effectiveness ratio is far below accepted thresholds for the one commonly used.

The intervention is of reasonable cost and effectiveness in the model. This is contributed by one important factor: the incremental treatment cost is relatively low. An annual cost of $1,509 to get people's hypertension under control is fairly small compared to the lifetime cost of compliance. However, it is worth to mention that we made a strong assumption that a current routine care sufficiently achieves the reduction of uncontrolled hypertension risk. Since there are many alternative interventions can be implemented to reduce the risk, the costs of different intervention would vary. In the study we select an annual incremental medical care cost as a conservative estimate. To avoid the potential bias due to the cost estimate variation, we also estimated the maximum cost of a cost-effective intervention given an assumed acceptable ICER value. We assumed an acceptable cost-effectiveness ratio of $50,000/QALY. Then we fixed the ICER value at that value and ran the model with changing intervention cost of hypertension care until ICER stops at the fixed value. We found that, if $50,000/QALY is an acceptable ICER, we can spend up to $13,910 per person/year before the ICER reach the value.

In the analysis, the cost-effectiveness ratio is independent of the percent of people that switch. Because the switchers are assumed to be a random sample of the population, the cost and health benefit of the switch is proportional to the percent of change. Switching one more percent will result in the increase of intervention cost, which will be proportional to the increase of the health benefit. In other words, the marginal rate is flat for any percentage of risk reduction. However, a 50 percent of risk reduction is not a

random pick. Several cohort studies have shown that it is practically feasible to achieve a fifty percent of risk reduction though appropriate interventions (1990).

Our analysis is subject to several limitations. Firstly, the results presented in the study should be considered hypothesis generating. The scenario set in this study is nevertheless highly hypothetical. Although several clinical trials demonstrated it is feasible to reduce the incidence of uncontrolled hypertension by fifty percent, there are certainly practical barriers to generalize it to population level. Moreover, we assumed a regular treatment will sufficiently achieve the blood pressure target and based our costing analysis on that. Second, our results are based on a simulation model that was built using estimates from the literature rather than the results of a prospectively conducted trial. Many of our model parameters have not been rigorously tested.

The second limitation is attributable to the model simplification. The simulation under current form does not specifically models the screening on high blood pressure. Therefore we did not include the undiagnosed hypertensive population in our analysis. This simplification results an exclusion of nearly 30% of the hypertensive population. Screening on hypertension is usually cheap and accurate. Because more early cases could be found and to benefit from the intervention, we expect current result underestimates the benefit of early stage hypertension control. Thirdly, although the analysis is conducted from the perspective of society, we did not estimate the indirect cost of the diseases in the model, such as loss of productivity, which could substantially contributes to the burden of CKD. The major reason we exclude the cost is that we did not found reliable estimate on

the indirect cost of CKD patients. Fourthly, we did not explicitly explore certain groups of population would be more likely to receive better care and control their blood pressure. The disparity of getting recommended cares and its effect on CKD outcome would be an interesting question in the need of further research.

Finally, we arbitrarily selected 30 years as the time horizon of simulation. While most of cost-effectiveness analyses are conducted using a life-time horizon, we did not extrapolate a longer period mainly due to the prediction uncertainty. A life-time horizon allows us to fully take into account the benefit of prolonged life due to the interventions. However, in our population level model, some of the model inputs might change considerably over time, as well as the treatment pattern and the associated costs. Nevertheless, in the model, nobody will have more than 30 years to accrue health benefits, and because reducing the rate of decline of GFR has effect over all the years from intervention to death, this time horizon will bias the cost-effectiveness estimate. To understand the time effect, we repeated the analysis for each 5 years interval starting from 10 years and we found a more favorable cost-effectiveness ratio with longer time period.

In summary, adherence to established blood pressure targets is low for both CKD and non-CKD population, despite growing evidence that control of hypertension reduce the incidence of CKD, and slow the decline of GFR. More aggressive campaigns focus on hypertension control in current CKD patients are needed, and the strategies to improve current practice on hypertensive control should be explored. Public health efforts should

be directed to identifying barriers of hypertension control in both CKD and general population. Our analysis shows the investment on the early prevention on hypertension cost can be recouped by deferring the extremely high costs of kidney failure, and improve the health outcomes of growing CKD population in the United States.

Acknowledgement: The initial support for this paper has come from the Charles Drew University/RAND/UCLA Comprehensive Center for Health Disparities in Chronic Kidney Disease U54 RR019234 NCRR/NIH. This is study is also generally supported by Pardee RAND Graduate School Kip and Mary Ann Hagopian dissertation award, and RAND Roybal Center for Health Policy Simulation.

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Appendix 3

Table 3-1 Health Conditions and Associated Medical Costs

	Annual Medical Cost	Sensitivity Range		Source
Incremental cost of hypertension care	$1,509	$1,009	$2,009	(Balu and Thomas, 2006)
Prescription Drugs	$730			
Inpatient visit	$458			
Outpatient visit	$153			
Emergency Room visit	$77			
Office-based medical visits	$51			
Home health visits	$22			
Other medical expenditure	$18			
Cost to initiate hypertension care	$0	$0	$1000	(Brosnan, et al., 2008; Silverberg, et al., 1974; Welch and Hill, 2002)
Diabetes	$16,881	$13,881	$19,881	(Hogan, et al., 2003)
CKD stage 1-3	$9,125	$4,125	$14,125	(Hogan, et al., 2002)
Dialysis	$66,192	$46,192	$86,192	(Hogan, et al., 2002)
Initial transplant	$129,459	$99,459	$159,459	(Hogan, et al., 2002)
Maintaining cost of functioning graft	$12,512	$7,512	$17,512	(Hogan, et al., 2002)
Death(last 6 months of life)	$37,361	$27,361	$47,361	(Hogan, et al., 2002)
Cardiovascular disease event	$7,433	$5,433	$9,433	(Hodgson and Cai, 2001)
Total living cost	$0	$0	$20,000	(Meltzer, 2001)

Table 3-2 Health Conditions and Associated Health Utilities

Condition	Utility Score	Sensitivity range		Source
CKD 1	0.98	0.96	1	(Boulware, et al., 2003)
CKD 2-3	0.92	0.89	0.95	(Boulware, et al., 2003)
CKD 4 dialysis	0.56	0.44	0.68	(Hogan, et al., 2002)
CKD 5 no transplant	0.53	0.43	0.63	(Boulware, et al., 2003)
CKD 5 with transplant	0.76	0.66	0.86	(Boulware, et al., 2003)
CVD	0.88	0.8	0.9	(Lamotte, et al., 2006)
DM	0.88	0.8	0.96	
Treated Hypertension				

age: 18-34	0.95	0.78	1	(Brunenberg, et al., 2007)
35-44	0.86	0.74	0.98	(Brunenberg, et al., 2007)
45-54	0.85	0.73	0.97	(Brunenberg, et al., 2007)
55-64	0.83	0.71	0.95	(Brunenberg, et al., 2007)
65-74	0.84	0.72	0.96	(Brunenberg, et al., 2007)
75 and older	0.82	0.71	0.93	(Brunenberg, et al., 2007)
Untreated Hypertension / None of above condition				
age: 18-34	0.98	0.9	1	*
35-44	0.89	0.771	1	(Anis, et al., 2006; Nagata-Kobayashi, et al., 2005)
45-54	0.88	0.764	0.996	(Anis, et al., 2006; Nagata-Kobayashi, et al., 2005)
55-64	0.86	0.745	0.975	(Anis, et al., 2006; Nagata-Kobayashi, et al., 2005)
65-74	0.87	0.75	0.99	(Anis, et al., 2006; Nagata-Kobayashi, et al., 2005)
75 and older	0.85	0.73	0.97	(Anis, et al., 2006; Nagata-Kobayashi, et al., 2005)

*: the age of the sample in Fryback et al starts from 35, so we assume a value of 0.98 for age group 18-34.

Table 3-3 Comparison between model predictions and actual mortality
rate per thousand

	All		**white male**		**white female**		**black male**		**black female**	
Age Group	**Obs**	**Model**	**Obs**	**Model**	**Obs**	**Model**	**Obs**	**model**	**obs**	**model**
35-39	1.6	2.3	1.9	0.6	2.9	2.5	2.2	2.2	3.7	3.5
40-44	2.4	3.3	2.8	3.0	4.3	4.0	3.3	4.1	5.5	5.6
45-49	3.6	3.9	4.2	3.8	6.8	9.1	5.1	5.0	8.8	9.7
50-54	5.2	6.2	6.0	6.3	9.7	10.1	7.0	7.2	13.0	17.9
55-59	8.0	9.5	9.4	8.1	13.7	11.8	9.9	9.5	18.5	18.1
60-64	12.6	11.2	14.8	16.6	19.5	20.6	14.9	22.9	25.7	23.0
65-69	19.3	18.9	23.3	22.9	26.6	25.8	21.4	27.2	33.7	32.8
70-74	29.7	31.3	36.3	37.9	39.8	34.4	32.9	34.3	49.6	57.3
75-79	45.6	45.4	55.2	55.6	58.0	64.2	49.4	53.9	71.4	73.6
80-84	74.0	73.5	89.6	93.9	85.2	89.3	75.6	59.7	102.5	99.2
85 and older	153.2	159.6	169.0	160.8	147.5	166.3	144.4	139.7	154.9	161.2

Note: observed data is obtained from National Vital Statistics Report 2005. www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_10.pdf accessed on March 2009.

Table 3-4 Reduction of the adverse health outcomes due to the intervention

Adverse Events	**10 Years**	**15 Years**	**20 Years**	**25 Years**	**30 Years**
ESRD	32.2	74.1	122.2	170.5	224.2
Dialysis	77.4	158.2	242.9	308.6	368.1
Transplant	1.9	16.3	30.6	38.1	56.6
Cardiovascular disease	42.2	90.6	127.9	192.7	248.0
Death	16.1	34.7	46.9	58.6	70.1

note: all the numbers are reported in thousand

Table 3-5 Cost-Saving on the adverse health outcomes of CKD due to the intervention

Adverse Events	10 Years	15 Years	20 Years	25 Years	30 Years
Dialysis	513	1,047	1,608	2,043	2,436
Transplant	26	239	559	858	1,257
Cardiovascular disease	314	673	950	1,433	1,844
Death	60	130	175	219	262
All	913	2,089	3,292	4,552	5,799

note: all the costs are reported in $million

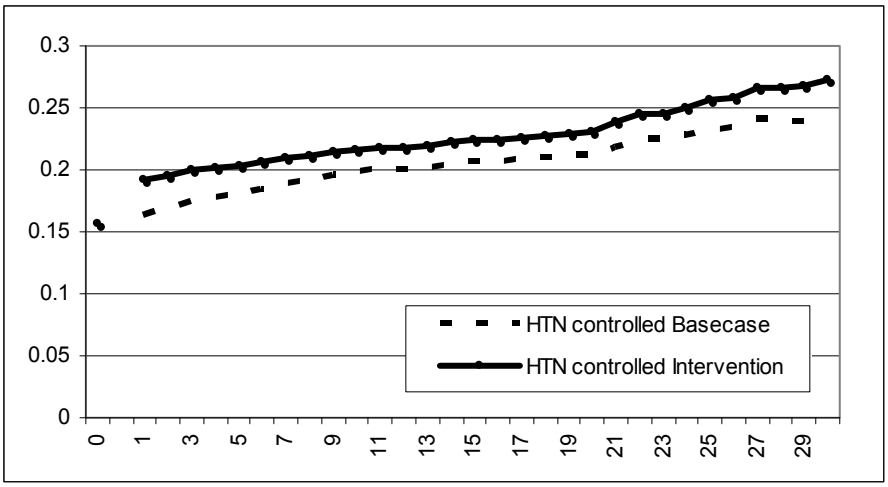
Table 3-6 Cost-Effectiveness Ratio: Base-case Analysis

	Status quo	Intervention	Difference
Unadjusted life years	16.58	16.61	0.03
QALY	15.07	15.35	0.28
Cost ($)	71,440.88	70,651.28	-789.60

Table 3-7 Cost-Effectiveness by different time horizons

	10 Years	15 Years	20 Years	25 Years	30 Years
Incremental Cost	2,968.3	2,410.0	1,769.0	607.4	-789.6
Incremental QALY	0.11	0.16	0.20	0.24	0.28
Incremental CE ratio	27,472.5	15,447.1	8,799.6	2,506.9	

Figure 3-1 The predicted prevalence of controlled hypertension among age 38 and older


0.3
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HTN controlled Basecase
HTN controlled Intervention

Figure 3-2 The predicted prevalence of uncontrolled hypertension among age 38 and older

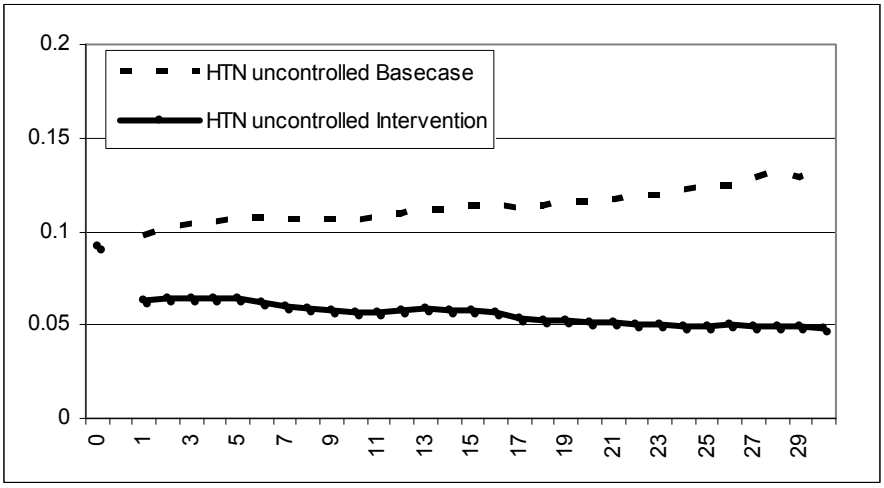

Figure 3-3 The predicted prevalence of all stage CKD among age 38 and older

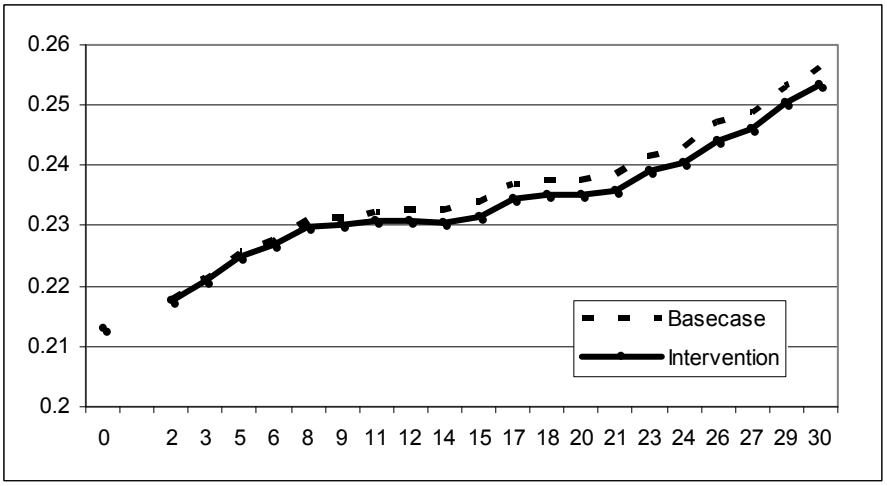

Figure 3-4 The predicted prevalence of CKD stage 4 among age 38 and older

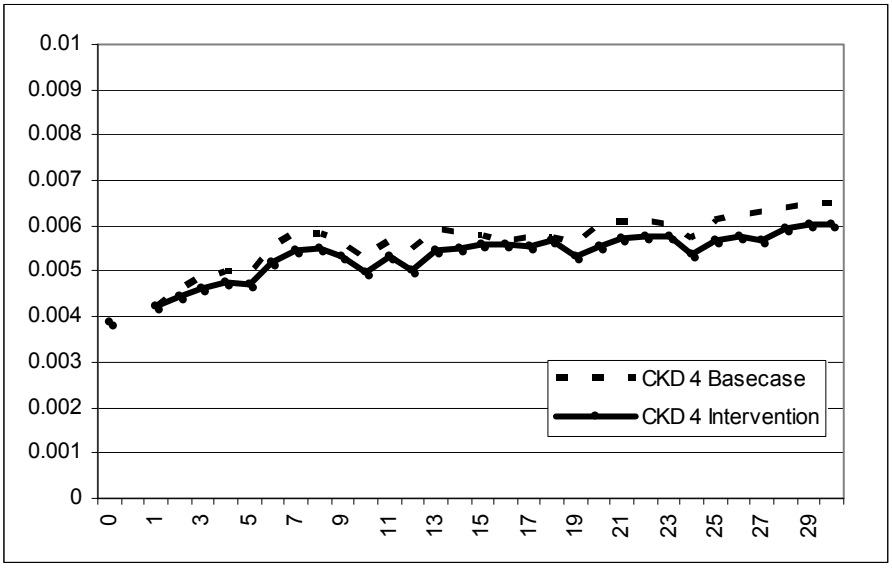

Figure 3-5 The predicted prevalence of CKD stage 5 among age 38 and older

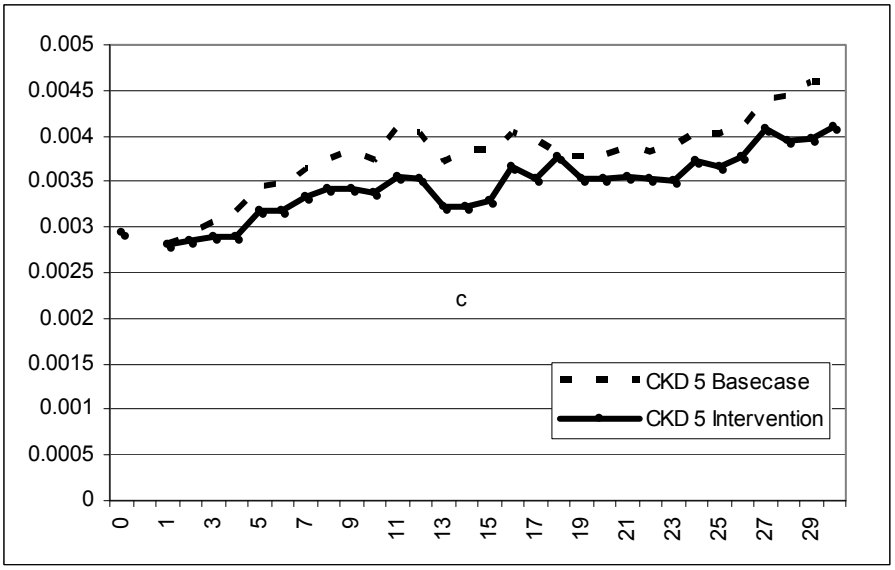

Figure 3-6 Sensitivity Analysis of Cost Parameters

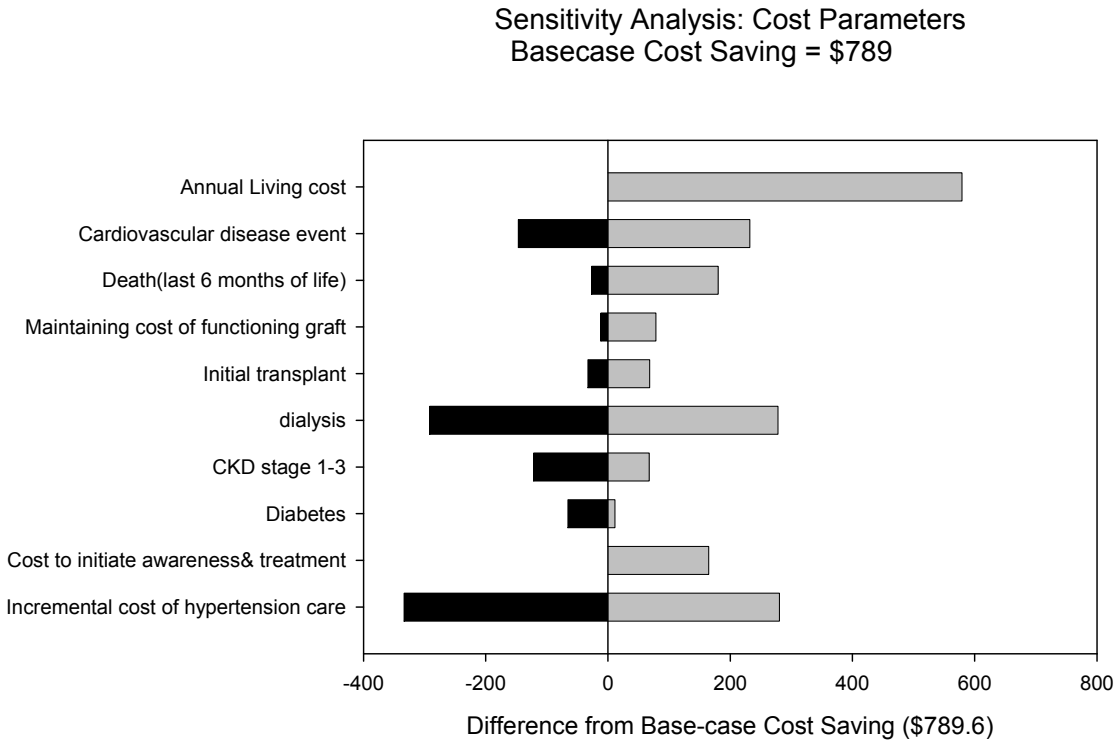

Figure 3-7 Sensitivity Analysis of Health Utility Parameters