***Project Title:***Are Medication Costs Killing Patients? Cost-Related Non-adherence and All-Cause Mortality in Patients with Chronic Illness.

**INTRODUCTION AND OBJECTIVES**

Diabetes and cardiovascular disease (CVD) currently affect 15% and 13% of United States (U.S.) adults, respectively.1,2 These conditions are the seventh and first leading causes of death in the U.S.,3 and though progress has been made in reducing incidence and mortality of cardiovascular disease,4,5 diabetes incidence is increasing, particularly among younger age groups.1,6

Beyond the substantial human cost, diabetes and CVD are associated with significant economic burden. Together, diabetes and CVD accounted for nearly $200 billion in personal healthcare costs in the U.S. in 2013, a figure which increased to $283 billion when also accounting for treatment of hypertension, a common risk factor for heart disease.7 Moreover, expenditures are expected to grow in the coming decades, largely due to the aging of the population and increased number of years lived with disease.2,8–10 A substantial portion of these costs will come from prescription drug expenditures, as drug prices in the U.S. are two to three times higher than in other industrialized nations.11,12 Currently, 57.6%, 11.3%, and 41.2% of diabetes, CVD and hypertension costs, respectively, are from medication expenditures, and these costs are continuing to grow at a rate of 5-6% annually.7 Although exponential price increases have been most clearly demonstrated for insulin, for which cost has risen more than six-fold since 2000,13,14 they are by no means unique to diabetic medications.

Although the overall health economy is impacted by rising drug prices, the high cost of medication primarily affects patients. Among persons with diabetes or hypertension, cost is the most common reason for medication nonadherence, with more than two-thirds of patients reporting skipping or delaying medication use due to financial barriers.15 These behaviors, along with neglecting to fill prescriptions to make medication last longer and taking less medication than prescribed, are collectively referred to as ‘cost-related nonadherence’ (CRN).16 Although CRN may result in short-term cost savings, nonadherence is associated with an increase in U.S. healthcare spending of $1,000 to $8,000 per patient, primarily due to a greater frequency of inpatient hospitalizations and emergency department visits.17–21

The prevalence of CRN among patients with chronic conditions is substantially higher than that of the general population.22 For instance, in comparison to the 6-7% of U.S. adults who reported at least one form of CRN in 2016,22 a 2018 survey of 627 U.S. adults with Type 1 diabetes found that more than 25% had rationed insulin in the previous year to manage costs, with 3.2% of patients rationing insulin on a daily basis and 38.6% decreasing use of blood glucose testing equipment to manage costs.23(p1) A 2017 study by Herkert and colleagues including both Type 1 and Type 2 diabetics seen at an outpatient clinic reported similar prevalence of CRN, and found that 40% of patients with non-adherence did not discuss underuse with their physician.23,24 Mixed samples of U.S. Medicare patients with hypertension, diabetes, and CVD reported slightly lower CRN, typically ranging from 7-10%.25,26 However, these studies were limited by possible selection bias and non-representative samples. In each of the studies focused on patients with diabetes, survey respondents were not randomly sampled and are likely systematically different from those without consistent access to care or health insurance. Similarly, older adults with Medicare, by definition, have better insurance coverage and medication benefits than the general U.S. population, and therefore do not reflect the healthcare experiences of younger, less insured adults.

Despite its high prevalence, few studies have investigated the medical implications of CRN. In general, non-adherence is associated with greater risk for hypertension, hypercholesterolemia, elevated hemoglobin A1C levels, and mortality in diabetics,24,27,28 and with greater risk for dyslipidemia, extended hospitalizations, and mortality in patients with hypertension or CVD.29–31 Yet, because previous studies documenting the adverse consequences of medication non-adherence have not specified reasons for non-adherence, it is unclear how CRN specifically contributes to these outcomes. The aims of this study are a) to assess the prevalence of CRN in a representative sample of U.S. adults with diabetes, hypertension, and/or CVD and b) to determine whether CRN is associated with higher risk of mortality in U.S. adults with diabetes, hypertension, and/or CVD.

**METHODS**

**Source Data**

This secondary analysis used publicly available data from the National Health Interview Survey (NHIS).32 The NHIS is a cross-sectional, population-representative multi-stage probability sample of non-institutionalized U.S. adults administered annually by the National Center for Health Statistics.33 Briefly, all interviews were conducted using computer-assisted personal interviews by trained U.S. Census Bureau staff, and consisted of two parts: 1) the ‘core’ questionnaire and 2) supplemental questions. The core questionnaire consisted of four subsections (Household, Family, Sample Adult, and Sample Child) which broadly assess basic demographic information, health status, healthcare access and utilization, and health behaviors. Supplemental questions vary from year to year to assess current health issues, and have included topics such as in-depth healthcare utilization and insurance information, cancer screening, and mental health.33 Questions relating to CRN were introduced into the survey in 2000, thus, in the current study we included data from the 2000 to 2014 waves only .

*Study Sample*

We restricted our study sample to individuals age 18 and over with diabetes, hypertension, and/or CVD for this secondary data analysis. Diabetes diagnosis was ascertained through a single item, asking whether participants had been told by a medical professional that they had “(Other than during pregnancy) diabetes or sugar diabetes?” (*N* = 39,571). We operationalized CVD as a diagnosis of one or more of the following: “a heart attack (sometimes called myocardial infarction?” (*N* = 16,142), “angina pectoris?” (*N* = 11,064), “coronary heart disease (CHD)?” (*N* = 21,005), or “any kind of heart condition other than coronary heart disease, angina pectoris, or a heart attack?” (*N* = 35,016) or “any kind of stroke?” (*N* = 13,214). In total, there were 61,968 respondents with CVD. Additionally, we considered an alternate classification of CVD including diagnosis of hypertension (*N* = 133,967); under this expanded definition a total of 156,892 participants were considered to have CVD.

**Measures**

*Primary Exposure*

Our primary exposure of interest was CRN. Because CRN was assessed differently in the NHIS before and after 2010, we harmonized data to generate a single dichotomous variable representing whether a participant had experienced CRN in the previous year. From 2000 to 2009, we operationalized CRN as a positive response to the single item asking whether participants had needed, but could not afford, medication in the previous year. From 2010 to 2014, participants were asked about additional specific CRN behaviors, thus we operationalized CRN as any affirmative response to items asking participants whether, in order to save money, they had 1) skipped medication doses, 2) taken less medicine than prescribed, or 3) delayed taking medicine in the last year. Although three other questions about cost-related barriers to medication use (“asked doctor for cheaper medication”, “obtained medication from foreign country”, “used alternative medication”) were also assessed in the NHIS, these were not included as CRN measures given that they represent substitution, rather than abstinence, behaviors. Further, a previous factor analysis showed that the latter three questions do not significantly load onto an adherence factor.34

*Outcome Measures*

The two primary outcomes for this analysis were all-cause and disease-specific mortality. Vital status through December 2015 was determined through probabilistic record linkage to the National Death Index. Respondents younger than age 18 and those providing insufficient identifying information were not eligible for linkage. Given that ineligible individuals may differ systematically from those who are eligible, we applied mortality-specific weights to all-cause and disease-specific mortality analyses to correct for possible selection bias. Further, as the public use data provides only year and quarter of death rather than exact dates, we calculated follow-up time as the span between date of interview and the last day in the quarter and year of death, when vital status was ascertained. For surviving individuals, follow-up time was censored at December 31, 2015. We excluded ten participants with diabetes (0.0007 %) and eight participants with heart conditions or CVD (0.0003 %) from analyses because recorded death dates occurred prior to interview dates.

*All-cause mortality*

We operationalized all-cause mortality as defined as any positive record of death in the National Death Index.

*Disease-specific mortality*

Probabilistic linkage between participant records and the National Death Index was used by staff at the National Center for Health Statistics to determine leading and contributing causes of death for all participants with recorded mortality events. We defined disease-specific deaths due to diabetes as those in which diabetes (ICD-10 codes E10 – E14) was listed as the primary cause of death and those in which diabetes was flagged as a contributing cause of death by probabilistic record linkage. We included two definitions of disease-specific deaths for individuals with CVD, depending upon whether the definition of CVD was expanded to include hypertension. For the narrower definition, we operationalized disease-specific deaths due to CVD as those in which the leading cause of death was listed as diseases of the heart (ICD-10 codes I00-I09, I11, I13, I20-I51) or cerebrovascular diseases (ICD-10 codes I60 – I69). For the expanded definition of CVD including hypertension, we operationalized disease-specific deaths as all causes listed in the narrow definition as well as essential hypertension and hypertensive renal disease (ICD-10 codes I10, I12, and I15). We defined disease-specific mortality separately by condition of interest such that individuals with a history of more than one condition (e.g. diabetes and hypertension) were only considered to have the outcome in analyses where the listed cause of death matched the primary disease of interest. For example, if an individual with both diabetes and CVD had diabetes listed as the primary cause of death, we considered them to have disease-specific morality in diabetes analyses but not in CVD analyses.

*Statistical Analyses*

We compared baseline demographic characteristics of participants with and without CRN using design-based χ2 and Wilcoxon signed rank tests for categorical and continuous variables, respectively. We used Cox proportional hazard regressions to assess the associations between CRN and all-cause and disease specific mortality risks among individuals with diabetes or CVD. Consistent with our operationalization of CVD, we modelled associations between CRN and mortality among two subsamples of participants with CVD: one, among those who met criteria for the narrow definition of stroke or any heart condition, excluding hypertension, and two, among those who met criteria under the expanded definition of stroke or any heart condition, including hypertension.

For all-cause mortality, we first fit an unadjusted model including only CRN, then adjusted for age, sex, insurance (private, public, Medicare, other, or none), race (white, Black or African American, Hispanic or Latino, Asian, or other), education (≤ high school, some college, college degree or greater), and diagnoses of other chronic conditions: cancer (all models), diabetes (CVD models only), hypertension (diabetes and CVD models not including hypertension) and CVD (diabetes models only). We selected adjustment variables using a directed acyclic graph as those with known or suspected confounding relationship between CRN and mortality (Supplemental Figure 1a).35–37 Similarly, to estimate the unadjusted and adjusted association between CRN and disease-specific mortality, we first fit a model including only CRN then, adjusted for all confounders in all-cause mortality models except presence of additional chronic conditions (Supplemental Figure 1b). Unless otherwise noted, hazard estimates for CRN represent the total, rather than the direct, effect of CRN on mortality, and we present coefficients for confounders as supplementary data because these estimates cannot typically be interpreted as either the direct or total effects of covariates on mortality.38 Among participants with diagnoses of diabetes or CVD who were eligible for linkage to the National Death Index, fewer than 1% were missing data on covariates, and cases with missing data were deleted listwise.

Additionally, we conducted a sensitivity analysis by stratifying at year of interview (≤ 2010, > 2010) to determine if the change in measurement of CRN in 2010 substantially impacted findings. We evaluated models for presence of influential observations and multicollinearity using standardized dfbeta values, and variance inflation factors, respectively, tested for proportional hazards using scaled Schoenfeld residuals,39 and assessed log-linearity of by plotting Martingale residuals against continuous predictors (i.e. age). In instances where models did not meet assumptions, we performed further sensitivity analyses to assess the robustness of results against violations: for influential observations, we deleted suspected influential cases and then refit models, for log-linearity, we inspected plots for points at which the log-hazard deviated from linearity and refit models using natural splines at inflection points. All analyses were conducted in R, version 3.6.1,40 and RStudio, version 1.2.5019.41 Cox models were performed using the *survival* package,42 and, to account for the complex sampling methodology of the NHIS, all regressions and descriptive statistics were adjusted for survey design using the *survey* package43.

**Results**

*Descriptive Statistics*

The final analytic sample sizes were 34,839 for diabetes, 53,009 for CVD excluding hypertension, and 128,723 for CVD including hypertension. Twenty percent of participants with diabetes reported at least one form of CRN, as did 19.1% of participants with CVD and 17.2% of participants with CVD including hypertension. As depicted in Table 1, among participants reporting CRN, the most common form of nonadherence was needing but not being able to afford medication (86 - 88% for all three conditions), followed by delaying medication doses (68 – 70%), taking less medication than prescribed (56 – 58%), and skipping medication doses (53 – 56%). Among participants with information on specific forms of CRN, 37.8% reported all three CRN behaviors (delaying, taking less, and skipping medication), and 15.3% reported two CRN behaviors. Participants with CRN were significantly younger and had higher BMIs than those without CRN, and were more likely to be female, non-white, or current smokers (all *p* < 0.001). Although participants with CRN were less likely to be insured than those without CRN, the most common form of insurance among those with CRN was private insurance (Table 1). Income and education were also significantly associated with CRN (both *p* < 0.001) such that approximately 50% of individuals reporting CRN had annual household incomes of less than $20,000 and 55% had a high school degree or less, compared to 27% and 46% of those without CRN, respectively. Individuals with CRN were more likely to live in the South and less likely to live in the Northeast than individuals without CRN, while the proportions of individuals living in the Midwest or West did not significantly differ by CRN status (Table 1).

**All-cause Mortality**

*Diabetes*

Among individuals with diabetes, 8,909 (23.6%) died of any cause during the follow-up period, 1,086 (12.2%) of whom reported CRN. The median follow-up time among individuals with diabetes was 291 weeks (IQR = 156 – 504). As shown in Table 2, the unadjusted hazard of all-cause mortality in individuals with CRN was 0.752 times (95% CI = 0.694 – 0.815) that of those without CRN. The direction of association between CRN and all-cause mortality was reversed after adjusting for potential confounders, such that CRN was associated with an 18.3% increase in the hazard of death (95% CI = 1.092 – 1.281) in individuals with diabetes relative to those without CRN. After stratifying by interview year, we found that among individuals with diabetes, the unadjusted association between CRN and all-cause mortality was higher and the adjusted association lower for individuals interviewed prior to 2011 relative to those interviewed in and after 2011 (unadjusted *p*interaction= 0.006; adjusted *p*interaction= 0.004, Table 2).

*Cardiovascular Disease*

The median length of follow-up for individuals with CVD, excluding hypertension, was 304 (IQR = 160 – 534). During that time, 16,345 (27.8%) of individuals categorized under the narrow definition of CVD died, 1,645 (10.1%) of whom reported CRN. CRN was associated with a 29.8% lower hazard of death (95% CI = 0.658 – 0.252) in the unadjusted model and a 14.8% increase in the hazard of death after adjustment (95% CI = 1.073 – 1.300) among individuals with CVD. The unadjusted hazard ratio of all-cause mortality for CRN was lower among those interviewed in and after 2011 compared to those interviewed before 2011 (*p*interaction < 0.001), while the adjusted hazard ratio did not significantly differ by interview period (*p*interaction = 0.149; Table 2).

*Cardiovascular Disease including Hypertension*

A total of 28,755 (19.5%) individuals classified as having CVD under the expanded definition died during the follow-up period, 2,698 (9.4%) of whom reported CRN. In unadjusted models, individuals with CVD or hypertension who experienced CRN had significantly lower hazard of death than individuals who did not experience CRN (HR = 0.771, 95% CI = 0.732 – 0.813). After adjustment for confounders, the hazard of death was 23.0% higher among individuals with CVD or hypertension who reported CRN relative to those who did not report CRN (95% CI = 1.163 – 1.300; Table 2). The unadjusted association between CRN and all-cause mortality was higher among those interviewed in and after 2011 (*p*interaction < 0.001), while the adjusted association was lower (*p*interaction = 0.040). A complete list of coefficients for included covariates in all-cause mortality models is listed in Supplementary Table 1.

**Disease-Specific Mortality**

*Diabetes*

Among individuals with diabetes, 3,045 (8.74%) died of diabetes during the follow-up period and of these individuals, 392 (12.9%) had experienced CRN. As shown in Table 2, CRN was associated with a 24.3% lower hazard of diabetes-related deaths before adjustment for confounders (95% CI = 0.674 – 0.870). However, after adjustment, the direction of association changed such that CRN was associated with a 22.6% higher hazard of diabetes-related deaths (95% CI = 1.074 – 1.399). The strength of association between CRN and diabetes-related mortality did not differ between those interviewed prior to versus in and after 2011 in either unadjusted (*p*interaction = 0.211) or adjusted (*p*interaction *=* 0.272) models, although the association was significant only among those interviewed in earlier waves.

*Cardiovascular Disease*

During follow-up, 4,845 (9.14%) of individuals with CVD, excluding hypertension, died due to heart or cerebrovascular disease, 449 (9.3%) of whom had reported CRN. CRN was associated with a lower hazard of disease-specific mortality in the unadjusted model. After adjusting for confounders, individuals with CVD who reported CRN had a 12.3% higher hazard of disease-specific mortality relative to individuals who did not report CRN, although this association was not significant (95% CI = 0.993 – 1.271; Table 2). When we stratified by year of interview, individuals interviewed prior to 2011 had a significantly lower unadjusted hazard of disease-specific mortality than those interviewed in and after 2011 (*p*interaction *=* 0.0179). The adjusted hazard of disease-specific mortality was not significantly different between the two strata (*p*interaction *=* 0.139).

*Cardiovascular Disease including Hypertension*

Under the expanded definition of CVD including hypertension, 10,321 (7.44%) of individuals with CVD died of disease-specific causes. Nine-hundred and twenty-seven (9.0%) of these individuals reported CRN. Before adjustment for confounders, CRN was associated with a 27.2% lower hazard of disease-specific mortality in those with CVD or hypertension (95% CI = 0.669 – 0.792). The direction of association was reversed in the adjusted model (Table 2). Although the unadjusted hazard of disease-specific mortality for CRN was lower in earlier waves of interviews compared to later waves (*p*interaction *=* 0.031), the adjusted hazard did not differ significantly by wave (*p*interaction *=* 0.220). In both strata, CRN among individuals with CVD and hypertension was associated with an approximately 30% higher hazard of disease specific mortality (Table 2, both *p* < 0.001). Supplementary Table 2 shows hazard ratios for all included confounders in disease-specific models.

**Model Assumptions**

We identified 121, 94, and 160 potentially influential cases in disease-specific diabetes, CVD, and CVD or hypertension models, respectively. Similarly, 78, 153, and 123 potentially influential cases were identified in all-cause diabetes, CVD, and CVD or hypertension models. Rao-Scott chi-square tests and Wilcoxon rank sign tests showed that potentially influential cases were older (median = 66 years, IQR = 55.50 - 81.00, *p*  < 0.001) and had shorter follow-up times (median = 233 weeks, IQR = 85 - 265, *p* < 0.001) than non-influential cases but did not differ in prevalence of CRN (32%, *p* = 0.208). Given that exclusion of potentially influential cases did not substantially change estimates (Supplementary Table 2), we retained these cases in final models. Models did not show evidence of multicollinearity (all VIFs < 1.5). Age displayed log-linearity with estimated hazards from 18 – 75 years, after which there was a non-linear increase in the risks of both all-cause and disease specific deaths. Refitting models using natural splines at age 75 did not change results, thus we report the simpler linear effects (Supplementary Table 3.) Finally, while the assumption of proportional hazards was met for CRN associated risks in all adjusted models, all models violated the proportional hazards assumption globally (all *p* < 0.001).

**Discussion**

In this secondary data analysis, we found that nearly one-fifth of persons with diabetes and CVD living in the United States experienced one or more forms of CRN in the previous year. Although CRN was associated with lower household income, lack of health insurance, and lower educational attainment, a substantial proportion of individuals unable to afford medication had insurance and incomes at or above the United States median. For years in which more than one survey item was used to assess CRN, we found that delaying taking medication was the most common strategy used to manage costs, though more than half of nonadherent patients reported multiple forms of CRN. Moreover, we demonstrate that CRN is associated with 15 – 30% higher risks of all-cause and disease-specific mortality among individuals with diabetes or CVD, including hypertension, although significant associations were only observed among those interviewed prior to 2011. Associations were of similar magnitude irrespective of chronic illness type and ultimate cause of death.

In most cases, hazards of CRN were subject to strong qualitative confounding. Given that younger individuals are at greater risk for CRN25 and, in general, a lower risk for mortality, we speculate that this variable played the strongest role in the inverse associations observed for unadjusted estimates, particularly when considered in conjunction with insurance status. Other confounders, such as education, and higher household income, were also significantly related to mortality, but are expected to be positive, rather than negative, confounders and would likely upwardly bias estimates.

Although the prevalence of CRN reported in this sample (~20%) is lower than estimates from community and clinical samples,23,24,34 it remains largely consistent with assessments from other nationally representative data, such as the Behavioral Risk Factor Surveillance Survey (BRFSS).44 Differences are likely due to community-level variations in socioeconomic factors as well as background prevalence of chronic disease and healthcare access. Similarly, while there is limited research on adverse outcomes associated with CRN, we note that the association between CRN and mortality in the present study is of similar magnitude to previous estimates for nonadherence generally,45,46 indicating that adverse effects of nonadherence may not vary according to reasons for nonadherence.

The lack of association between CRN and mortality in respondents interviewed after 2010 is also notable. Although we anticipated that CRN identified in 2011 and later would be associated with stronger mortality associations given the greater specificity in NHIS survey items,16 it may be that important dimensions of CRN were not captured by the new questions. Alternatively, the null findings may be a result of the shorter follow-up times and substantially lower sample size in the later survey years. Negative consequences of nonadherence depend on the disease, medication, and severity and duration of restriction,28,47 thus, it is possible that with longer follow-up we would observe similar risks of mortality in those interviewed before 2011. Finally, period effects such as the implementation of the Affordable Care Act in 2010 may have mitigated the risks associated with CRN, such as by increasing access to primary care physicians, prevention services, and Medicaid expansion.48–50 For instance, previous analyses have also shown lower rates of CRN and corresponding improvements in management of chronic disease among seniors following passage of the Affordable Care Act and closing of the Medicare Part D coverage gap.51,52

There most probable pathway through which CRN and higher mortality could be associated is increases in disease complications and severity. Inconsistent adherence has been shown to increase a variety of adverse outcomes in patients with diabetes and CVD, including retinopathy, nephropathy, microvascular complications,53 uncontrolled hypertension and coronary revascularization.30 In addition to direct effects of complications on mortality, greater disease severity often necessitates additional treatment regimens and higher financial costs, thereby potentially reinforcing the likelihood of CRN and additional adverse consequences. As noted elsewhere, from both a patient and provider standpoint, it is often more cost effective,54 though not necessarily cost-saving,55 to provide full prescription coverage to patients at risk of nonadherence than to treat future complications.

Though not necessarily motivated by net cost considerations, several states have begun to consider drug pricing policies that will make medication more affordable for individuals with diabetes. As of February 2020, two states (Colorado and Illinois) have instituted $100 monthly price caps on insulin payments, with 14 others (Connecticut, Florida, Kansas, Kentucky, New Jersey, Michigan, Massachusetts, New York, New Jersey, Pennsylvania, Virginia, Washington, West Virginia, Wisconsin, and Utah) considering similar legislation.56–62 At the federal level, the Prescription Drug Pricing Act of 2019 would redesign spending and reimbursement for Medicare Parts B and D, including penalties for medications with prices rising faster than inflation. Implicit in these policies is the assumption that lower prescription drug prices will have a positive impact on patients, potentially by decreasing financial burden, improving health, or both. However, the common counterargument is that price controls would have negative implications for pharmaceutical research and development both in the United States and abroad, although empirical evidence of this is mixed. Moreover, the effects of price controls are likely to be heterogenous with respect to different prescriptions, and as of yet, it is remains unclear how regulation of a single drug (i.e. insulin) will impact prices of other pharmaceuticals, patient adherence, and long-term outcomes. Though an evaluation of these policies was beyond the scope of the present analysis, our results generally support insulin regulation as a means to health improvement in individuals with diabetes, at least in relation to mortality, and that improvements would be especially pronounced among those with demonstrated financial need and high risk of CRN. Continued assessment is needed to monitor policy reach, effectiveness, and potential for translation to CVD, hypertension, and other chronic conditions.

The major strengths of our study were the use of a large and nationally representative sample, detailed adjustment for and identification of confounding variables, and thorough robustness checks for potential threats to internal validity. Given the nature of the sample, we were also able to investigate consequences of CRN in adults with all ranges of health insurance, including those covered through public and private sources. Previous analyses with comparable sample sizes to our study have been drawn limited to Medicare beneficiaries only,44–46 who are not representative of the younger population and may differ in medication adherence on other dimensions, such as positive medication values and beliefs.66,67

Still, our findings should be interpreted in light of several limitations. First, because interviews were conducted cross-sectionally, we only had access to a single assessment of CRN, leading to probable immortal time bias in our measure of the exposure. Participants who did not report CRN at baseline may have experienced CRN later in the follow-up period; conversely, those reporting CRN at baseline did not necessarily have difficulty affording medication throughout follow-up. Second, as discussed previously, due to the change in survey questions about CRN behaviors beginning in 2011, observed differences in hazard ratios by year of interview should be interpreted with caution. Inconsistencies could be an artifact of measurement error, shorter follow-up times, or period effects such as the passage of the Affordable Care Act.68,69 Similarly, our measurement of CRN was non-specific and may not have captured important variations in CRN behavior with consequences for mortality. For instance, respondents were also not asked about specific medications that they restricted or could not afford, so it is possible that individuals reporting CRN were adherent to crucial medications (e.g. insulin, statins) and non-adherent to others.70 However, lack of specificity in CRN measurement would likely bias results toward the null, as we expect that individuals with CRN to less critical medications would have better health outcomes than those who were nonadherent to essential prescriptions. Third, although the number of individuals with improbable death dates was low and we excluded all such cases, we acknowledge that the existence of cases with erroneous (negative) lengths of follow-up time in this study sample likely reduced the internal validity of mortality analyses. Nonetheless, we note that, one, the National Death Index is commonly used in studies of mortality and has been shown to have high sensitivity and validity when compared to other administrative records,71–73 and two, the percentage of anomalous records in our study sample ( < 0.001%) is lower than has been reported elsewhere.74

Altogether, our results suggest that CRN is a substantial risk factor for mortality in persons with chronic illness, and that efforts to address rising prescription drug costs may be valuable for increasing patient health and longevity. Efforts to increase medication affordability may be particularly beneficial for younger individuals and lower income communities, who are the greatest risk of CRN. Future studies should identify other long-term health implications of CRN and potential strategies to increase adherence in patients with limited financial access to medication.

**Competencies**

1. *Discuss the means by which structural bias, social inequities and racism undermine health and create challenges to achieving health equity at organizational, community and societal levels.* This project will address how social inequities in economic background and ability to pay for healthcare/medication contribute to disparities in chronic disease mortality by investigating the association of cost-related barriers to medication use and mortality and interpreting these effects in the discussion section of the paper.
2. *Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate.* This project will download, manage, and recode data from the National Health Interview Survey and conduct Cox regression, using R, to determine the association between CRN and mortality.
3. *Communicate audience-appropriate public health content, both in writing and through oral presentation.* Following data analysis, a publication-quality manuscript will be drafted and disseminated through appropriate scientific channels (i.e. submitted to peer review for publication).
4. *Interpret results of data analysis for public health research, policy or practice.* In the results and discussion sections of the manuscript, the results of analyses as well as implications for the U.S. healthcare system will be explained and contextualized for readers.
5. *Apply and interpret common statistical methods for inference (e.g., ANOVA, linear and logistic regression, survival analysis) found in public health studies.* Cox regression will be conducted to determine if CRN is associated with mortality in different subsamples of patients with chronic disease, and results will be explained using plain English within both the results and discussion sections of the manuscript.
6. *Demonstrate an understanding of systematic biases (selection and information biases) that affect observational, quasi-experimental, and experimental studies.* Potential sources of bias and other threats to study validity will be discussed in the limitations section of the manuscript, and efforts to minimize or control for bias will be reported in the methods section.
7. *Demonstrate an understanding of the components of reproducible research.* Code for analysis will be documented with comments and uploaded regularly onto GitHub as changes are made such that others will be able to understand and reproduce analyses. In the methods section of the manuscript, all procedures and analytic decisions will be clearly described such that other researchers could replicate results and build off them in future studies.

**Timeline**

11/8/2019 – 11/22/2019: Write IRB Proposal (Submit by end of period)

11/23/2019 – 11/30/2019: Write in depth introduction for Project Proposal

11/30/2019 - 12/05/2019: Edit Project Proposal for Final Submission + Prepare Oral Pitch

12/06/2019- Oral Pitch

1/13/2020 – 1/20/2020: Recode Variables/ Data Management

1/20/2020 – 1/27/2020: Generate Descriptive Statistics and Draft Table 1

1/28/2020 – 2/12/2020: Run Cox PH Analyses and Draft Table 2

2/13/2020 – 2/27/2020: Literature Review (w/ emphasis for discussion section)

2/13/2020 – 2/20/2020: Write Results Section

2/27/2020 – 3/11/2020: Write Discussion Section

3/11/2020 – 3/25/2020: Edit Manuscript + Reformat Intro/Methods from this proposal

3/25/2020 – 4/1/2020: Finalize draft

References

1. Menke A, Casagrande S, Geiss L, Cowie CC. Prevalence of and trends in diabetes among adults in the United States, 1988-2012. *Jama*. 2015;314(10):1021-1029.

2. Khavjou O, Phelps D, Leib A. Projections of cardiovascular disease prevalence and costs: 2015–2035. *Am Heart Assoc*. 2016.

3. Murphy SL, Xu J, Kochanek KD, Arias E. Mortality in the United States, 2017. 2018.

4. Mozaffarian Dariush, Benjamin Emelia J., Go Alan S., et al. Heart Disease and Stroke Statistics—2016 Update. *Circulation*. 2016;133(4):e38-e360. doi:10.1161/CIR.0000000000000350

5. Ford ES. Trends in Predicted 10-Year Risk of Coronary Heart Disease and Cardiovascular Disease Among U.S. Adults From 1999 to 2010. *J Am Coll Cardiol*. 2013;61(22):2249-2252. doi:10.1016/j.jacc.2013.03.023

6. Imperatore G, Boyle JP, Thompson TJ, et al. Projections of Type 1 and Type 2 Diabetes Burden in the U.S. Population Aged &lt;20 Years Through 2050: Dynamic modeling of incidence, mortality, and population growth. *Diabetes Care*. 2012;35(12):2515-2520. doi:10.2337/dc12-0669

7. Dieleman JL, Baral R, Birger M, et al. US Spending on Personal Health Care and Public Health, 1996-2013. *JAMA*. 2016;316(24):2627. doi:10.1001/jama.2016.16885

8. Murray CJ, Abraham J, Ali MK, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *Jama*. 2013;310(6):591-606.

9. Bommer C, Sagalova V, Heesemann E, et al. Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030. *Diabetes Care*. 2018;41(5):963-970. doi:10.2337/dc17-1962

10. Zhang P, Zhang X, Brown J, et al. Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(3):293-301. doi:10.1016/j.diabres.2010.01.026

11. Kesselheim AS, Avorn J, Sarpatwari A. The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. *JAMA*. 2016;316(8):858-871. doi:10.1001/jama.2016.11237

12. OECD. *Health at a Glance 2015*.; 2015. https://www.oecd-ilibrary.org/content/publication/health\_glance-2015-en.

13. Hua X, Carvalho N, Tew M, Huang ES, Herman WH, Clarke P. Expenditures and prices of antihyperglycemic medications in the United States: 2002-2013. *Jama*. 2016;315(13):1400-1402.

14. Biniek JF, Johnson W. *Spending on Individuals with Type 1 Diabetes and the Role of Rapidly Increasing Insulin Prices*. Health Care Cost Institute; 2019.

15. McHorney CA, Spain CV. Frequency of and reasons for medication non‐fulfillment and non‐persistence among American adults with chronic disease in 2008. *Health Expect Int J Public Particip Health Care Health Policy*. 2011;14(3):307-320. doi:10.1111/j.1369-7625.2010.00619.x

16. Pierre-Jacques M, Safran DG, Zhang F, et al. Reliability of New Measures of Cost-Related Medication Nonadherence. *Med Care*. 2008;46(4):444. doi:10.1097/MLR.0b013e31815dc59a

17. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication Adherence Leads To Lower Health Care Use And Costs Despite Increased Drug Spending. *Health Affai Rs*. 2011:9.

18. Jensen GA, Li Y. Long-run health effects of cost-related non-adherence to prescribed medications among adults in late midlife: Long-run health effects, cost-related non-adherence. *J Pharm Health Serv Res*. 2012;3(2):85-93. doi:10.1111/j.1759-8893.2012.00087.x

19. Blanchard J, Madden JM, Ross-Degnan D, Soumerai SB. The Relationship Between Emergency Department Use and Cost-Related Medication Nonadherence Among Medicare Beneficiaries. *Ann Emerg Med*. 2013;62(5). doi:10.1016/j.annemergmed.2013.04.013

20. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*. 2018;8(1):e016982. doi:10.1136/bmjopen-2017-016982

21. Lloyd JT, Maresh S, Powers CA, Shrank WH, Alley DE. How Much Does Medication Nonadherence Cost the Medicare Fee-for-Service Program?: *Med Care*. 2019;57(3):218-224. doi:10.1097/MLR.0000000000001067

22. Kennedy J, Wood EG. Medication Costs and Adherence of Treatment Before and After the Affordable Care Act: 1999–2015. *Am J Public Health*. 2016;106(10):1804-1807. doi:10.2105/AJPH.2016.303269

23. T1International. *Costs and Rationing of Insulin and Diabetes Supplies: Findings from the 2018 T1International Patient Survey*.; 2018:1-16. https://www.t1international.com/media/assets/file/T1International\_Report\_-\_Costs\_and\_Rationing\_of\_Insulin\_\_Diabetes\_Supplies\_2.pdf. Accessed October 17, 2019.

24. Herkert D, Vijayakumar P, Luo J, et al. Cost-Related Insulin Underuse Among Patients With Diabetes. *JAMA Intern Med*. 2019;179(1):112-114. doi:10.1001/jamainternmed.2018.5008

25. Tong X, Chu EK, Fang J, Wall HK, Ayala C. Nonadherence to Antihypertensive Medication Among Hypertensive Adults in the United States─HealthStyles, 2010. *J Clin Hypertens*. 2016;18(9):892-900. doi:10.1111/jch.12786

26. Marcum ZA, Zheng Y, Perera S, et al. Prevalence and Correlates of Self-Reported Medication Non-Adherence among Older Adults with Coronary Heart Disease, Diabetes Mellitus, and/or Hypertension. *Res Soc Adm Pharm RSAP*. 2013;9(6). doi:10.1016/j.sapharm.2012.12.002

27. Ho PM, Rumsfeld JS, Masoudi FA, et al. Effect of Medication Nonadherence on Hospitalization and Mortality Among Patients With Diabetes Mellitus. *Arch Intern Med*. 2006;166(17):1836-1841. doi:10.1001/archinte.166.17.1836

28. Egede LE, Gebregziabher M, Echols C, Lynch CP. Longitudinal Effects of Medication Nonadherence on Glycemic Control. *Ann Pharmacother*. 2014;48(5):562-570. doi:10.1177/1060028014526362

29. Rasmussen JN, Chong A, Alter DA. Relationship Between Adherence to Evidence-Based Pharmacotherapy and Long-term Mortality After Acute Myocardial Infarction. *JAMA*. 2007;297(2):177-186. doi:10.1001/jama.297.2.177

30. Ho PM, Magid DJ, Shetterly SM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. *Am Heart J*. 2008;155(4):772-779. doi:10.1016/j.ahj.2007.12.011

31. Heisler M, Langa KM, Eby EL, Fendrick AM, Kabeto MU, Piette JD. The health effects of restricting prescription medication use because of cost. *Med Care*. 2004;42(7):626-634. doi:10.1097/01.mlr.0000129352.36733.cc

32. Lynn A. Blewett, Rivera Drew JA, King ML, Williams KCW. IPUMS Health Surveys: National Health Interview Survery, Version 6.4 [dataset]. 2019.

33. NHIS - About the National Health Interview Survey. https://www.cdc.gov/nchs/nhis/about\_nhis.htm. Published June 28, 2019. Accessed October 20, 2019.

34. Patel MR, Piette JD, Resnicow K, Kowalski-Dobson T, Heisler M. Social determinants of health, cost-related non-adherence, and cost-reducing behaviors among adults with diabetes: findings from the National Health Interview Survey. *Med Care*. 2016;54(8):796-803. doi:10.1097/MLR.0000000000000565

35. Bhuyan SS, Shiyanbola O, Deka P, et al. The Role of Gender in Cost-Related Medication Nonadherence Among Patients with Diabetes. *J Am Board Fam Med*. 2018;31(5):743-751. doi:10.3122/jabfm.2018.05.180039

36. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs. *Medicine (Baltimore)*. 2017;96(4). doi:10.1097/MD.0000000000005641

37. Heisler M, Wagner TH, Piette JD. Patient Strategies to Cope with High Prescription Medication Costs: Who is Cutting Back on Necessities, Increasing Debt, or Underusing Medications? *J Behav Med*. 2005;28(1):43-51. doi:10.1007/s10865-005-2562-z

38. Westreich D, Greenland S. The Table 2 Fallacy: Presenting and Interpreting Confounder and Modifier Coefficients. *Am J Epidemiol*. 2013;177(4):292-298. doi:10.1093/aje/kws412

39. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. *Biometrika*. 1994;81(3):515-526. doi:10.2307/2337123

40. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2019. https://www.R-project.org/.

41. R Studio Team. *RStudio: Integrated Development for R*. Boston, MA: RStudio, Inc.; 2019. http://www.rstudio.com/.

42. Therneau T, Lumley T. survival: Survival analysis. R package version 2.38-3. 2015.

43. Lumley T. Analysis of Complex Survey Samples. *J Stat Softw*. 2004;9(1):1-19. doi:10.18637/jss.v009.i08

44. Kang H, Lobo JM, Kim S, Sohn M-W. Cost-related medication non-adherence among U.S. adults with diabetes. *Diabetes Res Clin Pract*. 2018;143:24-33. doi:10.1016/j.diabres.2018.06.016

45. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. *Br J Clin Pharmacol*. 2014;78(4):684-698. doi:10.1111/bcp.12339

46. Gosmanova Elvira O., Lu Jun L., Streja Elani, Cushman William C., Kalantar-Zadeh Kamyar, Kovesdy Csaba P. Association of Medical Treatment Nonadherence With All-Cause Mortality in Newly Treated Hypertensive US Veterans. *Hypertension*. 2014;64(5):951-957. doi:10.1161/HYPERTENSIONAHA.114.03805

47. Cherry SB, Benner JS, Hussein MA, Tang SSK, Nichol MB. The Clinical and Economic Burden of Nonadherence with Antihypertensive and Lipid-Lowering Therapy in Hypertensive Patients. *Value Health*. 2009;12(4):489-497. doi:10.1111/j.1524-4733.2008.00447.x

48. Sommers BD, Gunja MZ, Finegold K, Musco T. Changes in Self-reported Insurance Coverage, Access to Care, and Health Under the Affordable Care Act. *JAMA*. 2015;314(4):366-374. doi:10.1001/jama.2015.8421

49. Rosenbaum S. The Patient Protection and Affordable Care Act: Implications for Public Health Policy and Practice. *Public Health Rep*. 2011;126(1):130-135. doi:10.1177/003335491112600118

50. Miller S, Altekruse S, Johnson N, Wherry LR. *Medicaid and Mortality: New Evidence from Linked Survey and Administrative Data*. National Bureau of Economic Research; 2019.

51. Kennedy JJ, Maciejewski M, Liu D, Blodgett E. Cost-Related Nonadherence in the Medicare Program: The Impact of Part D. *Med Care*. 2011;49(5):522-526.

52. Park YJ, Martin EG. Medicare Part D’s Effects on Drug Utilization and Out-of-Pocket Costs: A Systematic Review. *Health Serv Res*. 2017;52(5):1685-1728. doi:10.1111/1475-6773.12534

53. Fukuda H, Mizobe M. Impact of nonadherence on complication risks and healthcare costs in patients newly-diagnosed with diabetes. *Diabetes Res Clin Pract*. 2017;123:55-62. doi:10.1016/j.diabres.2016.11.007

54. Ito K, Avorn J, Shrank WH, et al. Long-term cost-effectiveness of providing full coverage for preventive medications after myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2015;8(3):252-259. doi:10.1161/CIRCOUTCOMES.114.001330

55. Choudhry Niteesh K., Patrick Amanda R., Antman Elliott M., Avorn Jerry, Shrank William H. Cost-Effectiveness of Providing Full Drug Coverage to Increase Medication Adherence in Post–Myocardial Infarction Medicare Beneficiaries. *Circulation*. 2008;117(10):1261-1268. doi:10.1161/CIRCULATIONAHA.107.735605

56. Roberts D, Donovan K, Priola K. *Reduce Insulin Prices*.; 2019. https://leg.colorado.gov/bills/hb19-1216.

57. Illinois General Assembly - Bill Status for SB0667. http://www.ilga.gov/legislation/BillStatus.asp?GA=101&DocTypeID=SB&DocNum=667&GAID=15&SessionID=108&LegID=116604. Accessed February 8, 2020.

58. House Bill 109 (2020) - The Florida Senate. https://www.flsenate.gov/Session/Bill/2020/109. Accessed February 8, 2020.

59. A5786. https://www.njleg.state.nj.us/2018/Bills/A9999/5786\_I1.HTM. Accessed February 8, 2020.

60. Michigan Legislature - House Bill 4701 (2019). http://www.legislature.mi.gov/(S(t0pchkesswpua5ra3nx2klwk))/mileg.aspx?page=GetObject&objectname=2019-HB-4701. Accessed February 8, 2020.

61. Bill Information - House Bill 1873; Regular Session 2019-2020. The official website for the Pennsylvania General Assembly. https://www.legis.state.pa.us/cfdocs/billInfo/billInfo.cfm?sYear=2019&sInd=0&body=H&type=B&bn=1873. Accessed February 8, 2020.

62. 2019 Senate Bill 340. https://docs.legis.wisconsin.gov/2019/proposals/sb340. Accessed February 8, 2020.

63. Madden JM, Graves AJ, Zhang F, et al. Cost-Related Medication Nonadherence and Spending on Basic Needs Following Implementation of Medicare Part D. *JAMA*. 2008;299(16):1922-1928. doi:10.1001/jama.299.16.1922

64. Kennedy J, Tuleu I, Mackay K. Unfilled Prescriptions of Medicare Beneficiaries: Prevalence, Reasons, and Types of Medicines Prescribed. *J Manag Care Pharm*. 2008;14(6):553-560. doi:10.18553/jmcp.2008.14.6.553

65. Blumberg DM, Prager AJ, Liebmann JM, Cioffi GA, Moraes CGD. Cost-Related Medication Nonadherence and Cost-Saving Behaviors Among Patients With Glaucoma Before and After the Implementation of Medicare Part D. *JAMA Ophthalmol*. 2015;133(9):985-996. doi:10.1001/jamaophthalmol.2015.1671

66. Zivin K, Ratliff S, Heisler MM, Langa KM, Piette JD. Factors Influencing Cost-Related Nonadherence to Medication in Older Adults: A Conceptually Based Approach. *Value Health J Int Soc Pharmacoeconomics Outcomes Res*. 2010;13(4):338-345. doi:10.1111/j.1524-4733.2009.00679.x

67. Piette JD, Beard A, Rosland AM, McHorney CA. Beliefs that influence cost-related medication non-adherence among the “haves” and “have nots” with chronic diseases. *Patient Prefer Adherence*. 2011;5:389-396. doi:10.2147/PPA.S23111

68. Zeng F, Patel BV, Brunetti L. Effects of coverage gap reform on adherence to diabetes medications. *Am J Manag Care*. 2013;19(4):308—316.

69. Mulcahy AW, Eibner C, Finegold K. Gaining Coverage Through Medicaid Or Private Insurance Increased Prescription Use And Lowered Out-Of-Pocket Spending. *Health Aff (Millwood)*. 2016;35(9):1725-1733. doi:10.1377/hlthaff.2016.0091

70. Kurlander JE, Kerr EA, Krein S, Heisler M, Piette JD. Cost-Related Nonadherence to Medications Among Patients With Diabetes and Chronic Pain: Factors beyond finances. *Diabetes Care*. 2009;32(12):2143-2148. doi:10.2337/dc09-1059

71. Skopp NA, Smolenski DJ, Schwesinger DA, Johnson CJ, Metzger-Abamukong MJ, Reger MA. Evaluation of a methodology to validate National Death Index retrieval results among a cohort of U.S. service members. *Ann Epidemiol*. 2017;27(6):397-400. doi:10.1016/j.annepidem.2017.05.004

72. Wojcik NC, Huebner WW, Jorgensen G. Strategies for Using the National Death Index and the Social Security Administration for Death Ascertainment in Large Occupational Cohort Mortality Studies. *Am J Epidemiol*. 2010;172(4):469-477. doi:10.1093/aje/kwq130

73. Lash T, Silliman R. A Comparison of the National Death Index and Social Security Administration Databases to Ascertain Vital Status. *Epidemiology*. 2001;12(2):259-261.

74. Fillenbaum GG, Burchett BM, Blazer DG. Identifying a National Death Index Match. *Am J Epidemiol*. 2009;170(4):515-518. doi:10.1093/aje/kwp155

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Diabetes | | CVD | | CVD, including Hypertension | |
|  | CRN | No CRN | CRN | No CRN | CRN | No CRN |
| N (unweighted) 2000 -2014 |  |  |  |  |  |  |
| Age M(SD) |  |  |  |  |  |  |
| Male |  |  |  |  |  |  |
| BMI M(SD) |  |  |  |  |  |  |
| Region |  |  |  |  |  |  |
| Northeast |  |  |  |  |  |  |
| Midwest |  |  |  |  |  |  |
| South |  |  |  |  |  |  |
| West |  |  |  |  |  |  |
| Race/Ethnicity |  |  |  |  |  |  |
| White |  |  |  |  |  |  |
| Black |  |  |  |  |  |  |
| Hispanic/Latino |  |  |  |  |  |  |
| American Indian/Alaska Native |  |  |  |  |  |  |
| Asian |  |  |  |  |  |  |
| Other |  |  |  |  |  |  |
| Education |  |  |  |  |  |  |
| High School or Less |  |  |  |  |  |  |
| Some College |  |  |  |  |  |  |
| College Degree + |  |  |  |  |  |  |
| Household Income |  |  |  |  |  |  |
| <20k |  |  |  |  |  |  |
| 20-<35k |  |  |  |  |  |  |
| 35k-<60k |  |  |  |  |  |  |
| 60k- <80k |  |  |  |  |  |  |
| 80k -<100k |  |  |  |  |  |  |
| 100k + |  |  |  |  |  |  |
| Smoking Status |  |  |  |  |  |  |
| Never |  |  |  |  |  |  |
| Former |  |  |  |  |  |  |
| Current |  |  |  |  |  |  |
| Cost-Related Nonadherence |  |  |  |  |  |  |
| Needed but couldn't afford medication |  |  |  |  |  |  |
| Skipped medication doses\* |  |  |  |  |  |  |
| Delayed medication doses\* |  |  |  |  |  |  |
| Took less medicine than prescribed\* |  |  |  |  |  |  |
| Note: All numbers displayed in table are survey-weighted percentages (standard error). Bold face denotes statistically significant | | | | | | |
| differences (p < 0.05) between CRN and no CRN within each disease category, as determined by t-tests or Rao-Scott Chi-Square tests. | | | | | | |
| \*Indicates a survey item only included in 2010-2014 waves. | |  |  |  |  |  |

**Table 1.** Sample characteristics of 2000- 2014 National Health Interview Survey participants with diabetes, cardiovascular disease (CVD), and/or hypertension.

**Table 2.** Survey-weighted hazard ratios of disease-specific and all-cause mortality for cost-related nonadherence among National Health Interview Survey (2000- 2014) participants with diabetes, cardiovascular disease, and/or hypertension.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Disease Specific Mortality | | | |  | All-Cause Mortality | | | |
|  | Died: N (%) | Follow-Up Time, Weeks Median (IQR) | Model 1: HR (95% CI)1 | Model 2: HR (95% CI)2 |  | Died: N (%) | Follow-Up Time, Weeks Median (IQR) | Model 1: HR (95% CI)1 | Model 2: HR (95% CI)2 |
| **Full Sample** |  |  |  |  |  |  |  |  |  |
| CRN for Diabetes |  |  |  |  |  |  |  |  |  |
| CRN for CVD, excluding hypertension |  |  |  |  |  |  |  |  |  |
| CRN for CVD, including hypertension |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **2000-2010 Waves** | |  |  |  |  |  |  |  |  |
| CRN for Diabetes |  |  |  |  |  |  |  |  |  |
| CRN for CVD, excluding hypertension |  |  |  |  |  |  |  |  |  |
| CRN for CVD, including hypertension |  |  |  |  |  |  |  |  |  |
| 1. Unadjusted model. 2. Adjusted for age, sex, race, insurance status, region, smoking status, and body mass index. | | | | | | | |  |  |
| Abbreviations: CRN, cost-related nonadherence; CVD, cardiovascular disease; IQR, interquartile range; HR, hazard ratio. | | | | | | | |  |  |