Cost-Related Non-adherence and Mortality in Patients with Diabetes and Cardiovascular
Disease: A Multi-year Investigation Using the National Health Interview Survey

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I, Sarah Van Alsten, have neither given nor received any unauthorized assistance (as detailed in
the Brown School student handbook) in the completion of this work. I certify that the work is
authentically my own.

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 I included data from the 2000 to 2014 waves only .

Study Sample

I 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?" ($N = 39,571$). I 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, I 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, I harmonized data to generate a single dichotomous variable representing whether a participant had experienced CRN in the previous year. From 2000 to 2009, I 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 I 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, I 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, I 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. I 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. Figure 1 shows a conceptual model of the factors which contribute to CRN, and the proposed association between CRN and mortality.

All-cause mortality

I 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. I 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. I 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, I 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, I 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). I 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, I considered them to have disease-specific morality in diabetes analyses but not in CVD analyses.

Statistical Analyses

I compared baseline demographic characteristics of participants with and without CRN using design-based χ^2 and Wilcoxon signed rank tests for categorical and continuous variables, respectively. I 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, I 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, I 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 ($\leq$ 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). I selected adjustment variables using a directed acyclic graph as those with known or suspected confounding relationship between CRN and mortality (Supplementary Figure 1).[35–37] Similarly, to estimate the unadjusted and adjusted association between CRN and disease-specific mortality, I first fit a model including only CRN then, adjusted for all confounders in all-cause mortality models except presence of additional chronic conditions (Supplementary Figure 2). Unless otherwise noted, hazard estimates for CRN represent the total, rather than the direct, effect of CRN on mortality, and I 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, I conducted a sensitivity analysis by stratifying at year of interview ($\leq$ 2010, > 2010) to determine if the change in measurement of CRN in 2010 substantially impacted

findings. I 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, I performed further sensitivity analyses to assess the robustness of results against violations: for influential observations, I deleted suspected influential cases and then refit models, for log-linearity, I 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* package[43].

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, I 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). A complete

list of hazard ratios for confounders is show in Supplementary Table 1.

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). Supplementary Table 2 displays the estimated hazard ratios for all confounders.

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). The hazard ratios for confounders are listed in Supplementary Table 3.

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 ($p_{\text{interaction}}$ = 0.211) or adjusted ($p_{\text{interaction}}$ = 0.272) models, although the association was significant only among those interviewed in earlier waves. Supplementary Table 4 shows the hazard ratios for confounding variables.

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 I 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 ($p_{\text{interaction}}$ = 0.0179). The adjusted hazard of disease-specific mortality was not significantly different between the two

strata ($p_{\text{interaction}}$ = 0.139). Hazard ratios for associated confounders are displayed in Supplementary Table 5.

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 ($p_{\text{interaction}}$ = 0.031), the adjusted hazard did not differ significantly by wave ($p_{\text{interaction}}$ = 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 6 shows hazard ratios for all included confounders in the disease-specific mortality models for cardiovascular disease, including hypertension.

Model Assumptions

I 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 (22%, $p = 0.208$). Given that exclusion of potentially influential cases did not substantially change estimates (Supplementary Table 7), I 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 substantially change point estimate, thus I report the simpler linear effects (Supplementary Table 8). Finally, while the assumption of proportional hazards was met for the CRN coefficient in all adjusted models, all models violated the proportional hazards assumption globally (all $p < 0.001$).

Discussion

In this secondary data analysis, I 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, I 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, I 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 CRN[25] and, in general, a lower risk for mortality, I 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, I 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 I 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 I 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 co-payments,[56,57] with several others considering similar legislation.[58–62] 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.[63] Implicit in these policies is the assumption that lower prescription drug prices will have a positive impact on patients by decreasing financial burden, improving health, or both. The common counterargument is that price controls would have negative implications for pharmaceutical research and development,[64] however, these considerations should be balanced against the necessity of the drug (demand inelasticity) and availability of substitutes. In the case of insulin, a 100-year old drug that is essential for individuals with Type 1 diabetes and requires little capital outlay on the production side,[65] small reductions in innovation are likely justified by increasing prescription accessibility, especially for those in greatest financial need.[66] Moreover, most evidence has focused on the effects of reference pricing (limiting the price of a specific drug to a range within that of common competitors) rather than price caps (also called 'maximum pricing,' as in the proposed insulin legislation) and nearly all research has been conducted in European markets.[67] Though an evaluation of these policies was beyond the scope of the present analysis, our results do lend support to some form of price protection as a means to health improvement in individuals with diabetes, provided that caps are able to reduce CRN, and I are optimistic about the potential of new legislation to make access to essential care more equitable for patients most in need. Improvements would be especially pronounced among those with demonstrated financial need and high risk of CRN. Nonetheless, 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, I 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.[71,72]

Still, our findings should be interpreted in light of several limitations. First, because interviews were conducted cross-sectionally, I 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.[73,74] 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.[75] However, lack of specificity in CRN measurement would likely bias results toward the null, as I 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 I excluded all such cases, I 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, I 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,[76–78] and two, the percentage of anomalous records in our study sample ($< 0.001\%$) is lower than has been reported elsewhere.[79]

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 most likely to experience 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

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Figure 1. Conceptual model of relationship between cost related nonadherence and mortality. Components depicted in grey are assumed to be determinants of healthcare access and utilization (Anderson, 1968) while components shown in black are the primary focus of the current study. Skipping medication means forgoing medication doses altogether as a result of cost, substitution of medication means taking cheaper alternative medications, and delaying medication means delaying taking doses or waiting to fill prescriptions to make medication last longer and save money.
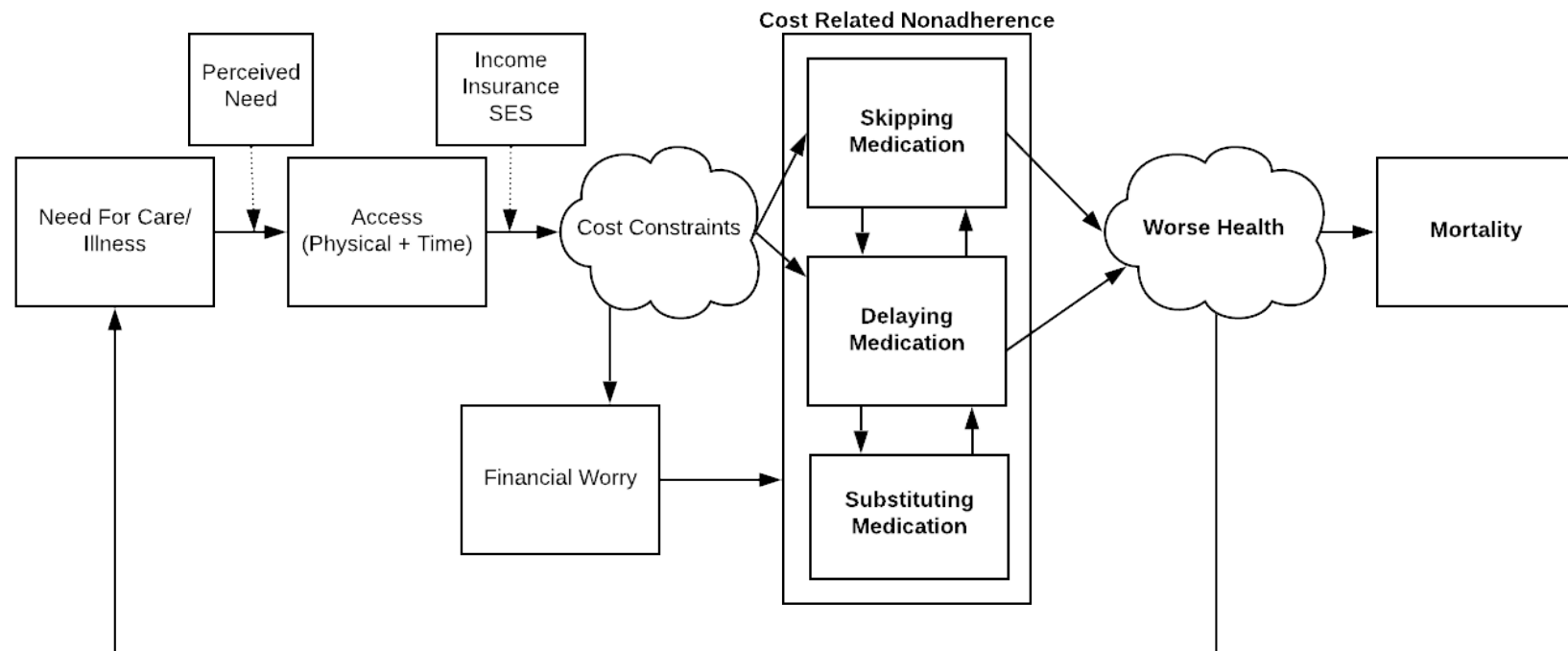
Table 1. Sociodemographic characteristics of 2000- 2014 National Health Interview Survey participants with diabetes, cardiovascular disease (CVD), and/or hypertension.

	Diabetes		CVD, excluding Hypertension		CVD, including Hypertension	
	CRN	No CRN	CRN	No CRN	CRN	No CRN
N (weighted) 2000 -2014	1872888.6 (19.9)	7521527.8 (80.1)	4311920.2 (19.1)	18276849.2 (80.9)	10364659.4 (17.2)	49886713.8 (82.8)
Age Median (IQR)	55.00 [46.00, 63.00]	64.00 [54.00, 73.00]	55.00 [45.00, 65.00]	67.00 [54.00, 77.00]	53.00 [42.00, 62.00]	62.00 [50.00, 74.00]
Female	779793.6 (61.2)	1071740.3 (52.2)	1178873.2 (62.2)	1535387.7 (50.7)	2653920.1 (62.9)	4260646.5 (53.5)
BMI Median (IQR)	31.10 [17.30, 54.50]	29.80 [16.10, 53.90]	28.20 [15.70, 54.50]	27.40 [14.80, 55.30]	29.00 [15.70, 54.50]	28.10 [14.80, 55.30]
Region						
Northeast	153906.2 (12.1)	362749.5 (17.7)	233900.1 (12.3)	546129.7 (18.0)	515853.1 (12.2)	1421081.4 (17.8)
Midwest	299530.7 (23.5)	485259.3 (23.6)	471369.1 (24.9)	743503.1 (24.5)	990868.0 (23.5)	1935019.0 (24.3)
South	588225.5 (46.2)	819511.7 (39.9)	846689.4 (44.7)	1165676.9 (38.5)	1948269.3 (46.2)	3073716.8 (38.6)
West	232115.0 (18.2)	385883.1 (18.8)	343579.6 (18.1)	574697.3 (19.0)	764312.7 (18.1)	1532803.4 (19.2)
Race/Ethnicity						
White	762645.3 (59.9)	1368077.9 (66.6)	1354773.1 (71.5)	2414174.9 (79.7)	2794604.7 (66.2)	5961428.7 (74.9)
Black	274570.6 (21.6)	319727.9 (15.6)	319393.8 (16.8)	314723.7 (10.4)	844987.7 (20.0)	1046326.7 (13.1)
Hispanic/Latino	196393.1 (15.4)	257571.8 (12.5)	171492.5 (9.0)	199751.8 (6.6)	463015.7 (11.0)	639574.3 (8.0)
American Indian/Alaska Native	15385.5 (1.2)	22876.9 (1.1)	25105.5 (1.3)	23328.1 (0.8)	44338.7 (1.1)	53119.3 (0.7)
Asian	21015.1 (1.6)	79854.6 (3.9)	20068.9 (1.1)	70387.3 (2.3)	60015.6 (1.4)	244833.0 (3.1)
Other	3767.9 (0.3)	5294.7 (0.3)	4704.3 (0.2)	7641.1 (0.3)	12340.8 (0.3)	17338.6 (0.2)
Health Insurance Coverage						
None	321969.8 (25.3)	96992.3 (4.7)	475956.7 (25.2)	111246.1 (3.7)	1285644.8 (30.6)	410375.3 (5.2)
Public Insurance (Medicaid/CHIP)	243829.1 (19.2)	397405.6 (19.4)	382161.9 (20.2)	498622.5 (16.5)	728162.3 (17.3)	1138810.5 (14.3)
Private	466939.6 (36.7)	1041669.2 (50.8)	618065.9 (32.7)	1590471.4 (52.6)	1492673.9 (35.5)	4573969.1 (57.5)
Military	18252.2 (1.4)	125139.6 (6.1)	35798.0 (1.9)	206855.3 (6.8)	61814.6 (1.5)	451068.5 (5.7)
Medicare	216756.3 (17.1)	384122.1 (18.7)	372219.3 (19.7)	616005.1 (20.4)	627517.9 (14.9)	1364089.1 (17.2)
Other	2921.4 (0.2)	5098.1 (0.2)	5174.3 (0.3)	3378.5 (0.1)	10847.1 (0.3)	12089.2 (0.2)
Education						
High School or Less	734748.8 (58.0)	1065573.4 (52.2)	1051034.3 (55.8)	1429955.7 (47.4)	2310737.6 (55.1)	3571093.8 (45.0)
Some College	386110.5 (30.5)	566380.7 (27.7)	608890.9 (32.4)	854274.1 (28.3)	1368270.2 (32.7)	2294780.0 (28.9)
College Degree +	145874.7 (11.5)	410085.9 (20.1)	222088.2 (11.8)	730832.0 (24.2)	511632.9 (12.2)	2063992.3 (26.0)

Household Income						
< $20,000	**574066.5 (45.1)**	**576371.3 (28.1)**	**949730.5 (50.1)**	**823869.0 (27.2)**	**1939293.9 (46.0)**	**1830836.8 (23.0)**
$20,000 to < $45,000	**323401.4 (25.4)**	**416123.4 (20.3)**	**459014.3 (24.2)**	**640813.9 (21.1)**	**1046478.0 (24.8)**	**1537042.2 (19.3)**
$45,000 to < $65,000	**243470.7 (19.1)**	**467633.0 (22.8)**	**314766.9 (16.6)**	**643604.9 (21.2)**	**776030.1 (18.4)**	**1761969.1 (22.1)**
$65,000 to < $85,000	**79488.3 (6.2)**	**224663.7 (10.9)**	**100902.7 (5.3)**	**314559.3 (10.4)**	**269453.2 (6.4)**	**939823.6 (11.8)**
$85,000 to < $100,000	**24359.3 (1.9)**	**120192.7 (5.9)**	**34169.3 (1.8)**	**193219.8 (6.4)**	**87039.1 (2.1)**	**605169.0 (7.6)**
$100,000 or more	**28991.3 (2.3)**	**248419.7 (12.1)**	**36954.3 (1.9)**	**413940.1 (13.7)**	**101008.8 (2.4)**	**1287779.9 (16.2)**
Smoking Status						
Never	**1248483.9 (45.3)**	**2267261.1 (52.4)**	**1449656.9 (37.6)**	**2796679.1 (46.0)**	**3761504.8 (42.7)**	**8691956.3 (52.3)**
Former	**786087.3 (28.5)**	**485042.3 (34.3)**	**1049201.6 (27.2)**	**2376857.2 (39.1)**	**2127650.7 (24.2)**	**5495561.7 (33.1)**
Current	**723574.5 (26.2)**	**571186.9 (13.2)**	**1355225.9 (35.2)**	**910527.1 (15.0)**	**2920187.5 (33.1)**	**2424061.0 (14.6)**
Cost-Related Nonadherence						
Needed but couldn't afford medication	2400453.7 (86.8)	0 (0.0)	3412747.5 (88.4)	0 (0.0)	7708209.7 (87.3)	0 (0.0)
Skipped medication doses*	1874447.0 (56.2)	0 (0.0)	2222249.2 (52.9)	0 (0.0)	5371382.6 (53.6)	0 (0.0)
Delayed medication doses*	2347292.6 (70.3)	0 (0.0)	2875838.6 (68.4)	0 (0.0)	6854083.4 (68.4)	0 (0.0)
Took less medicine than prescribed*	1932055.2 (57.9)	0 (0.0)	2339466.4 (55.7)	0 (0.0)	5652058.2 (56.4)	0 (0.0)

Note: All numbers displayed in table are survey-weighted N (%) unless otherwise indicated. 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 2. Associations of all-cause and disease-specific mortality with cost-related nonadherence among National Health Interview Survey (2000- 2014) participants with diabetes, cardiovascular disease, and/or hypertension.

	Follow-Up Time, Weeks Median (IQR)	All-Cause Mortality			Disease Specific Mortality		
		Died: N (%)	Model 1: HR (95% CI)[1]	Model 2: HR (95% CI)[2]	Died: N (%)	Model 1: HR (95% CI)[1]	Model 2: HR (95% CI)[3]
Full Sample							
CRN for Diabetes	291 (156 - 504)	8909 (23.6)	**0.752 (0.694 - 0.815)**	**1.183 (1.092 - 1.281)**	3045 (8.74)	**0.766 (0.674 - 0.870)**	**1.226 (1.074 - 1.399)**
CRN for CVD, narrow definition*	304 (160 - 534)	16345 (27.8)	**0.702 (0.658 - 0.750)**	**1.148 (1.073 - 1.228)**	4845 (9.14)	**0.618 (0.548 - 0.696)**	1.123 (0.993 - 1.271)
CRN for CVD, expanded**	322 (169 - 552)	28755 (19.5)	**0.771 (0.732 - 0.813)**	**1.230 (1.163 - 1.300)**	10321 (7.44)	**0.728 (0.669 - 0.792)**	**1.310 (1.196 - 1.434)**
2000-2010 Waves							
CRN for Diabetes	465 (360 - 652)	7379 (34.1)	**0.799 (0.731 - 0.875)**	**1.222 (1.112 - 1.345)**	2563 (13.0)	**0.809 (0.700 - 0.934)**	**1.289 (1.111 - 1.496)**
CRN for CVD, narrow definition*	474 (330 - 630)	13771 (37.4)	**0.734 (0.685 - 0.786)**	**1.180 (1.100 - 1.271)**	4282 (12.9)	**0.659 (0.582 - 0.747)**	**1.172 (1.028 - 1.334)**
CRN for CVD, expanded**	508 (360 - 652)	24440 (27.1)	**0.805 (0.760 - 0.852)**	**1.265 (1.190 - 1.346)**	9023 (10.7)	**0.758 (0.691 - 0.833)**	**1.326 (1.198 - 1.467)**
2011 - 2014 Waves							
CRN for Diabetes	165 (104 - 230)	1530 (9.50)	**0.681 (0.605 - 0.767)**	0.967 (0.800 - 1.173)	482 (3.20)	**0.779 (0.639 - 0.950)**	1.055 (0.779 - 1.430)
CRN for CVD, narrow definition*	161 (100 - 230)	2574 (11.77)	**0.620 (0.562 - 0.684)**	1.019 (0.868 - 1.195)	563 (2.84)	**0.768 (0.633 - 0.931)**	1.054 (0.757 - 1.468)
CRN for CVD, expanded**	165 (104 - 234)	4315 (7.53)	**0.695 (0.643 - 0.752)**	1.083 (0.940 - 1.245)	1298 (2.39)	**0.802 (0.700 - 0.918)**	**1.311 (1.051 - 1.634)**

Note: All hazard ratios are weighted for survey design. Disease specific mortality is defined as having a listed cause of death of diabetes, heart or cerebrovascular disease, or heart, cerebrovascular disease or underlying hypertension for diabetes, CVD, and CVD with hypertension models, respectively. Bold face denotes statistical significance. *The narrow definition of CVD includes heart attack, angina pectoris, coronary heart disease, other heart condition, or stroke. ** The expanded definition of CVD includes all conditions for the narrow definition or a diagnosis of hypertension. 1. Unadjusted Hazard Ratio. 2. Hazard Ratio 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). 3. Hazard ratio adjusted for age, sex, insurance (private, public, Medicare, other, or none), race (white, Black or African American, Hispanic or Latino, Asian, or other), and education (≤ high school, some college, college degree or greater). Abbreviations: CRN, cost-related nonadherence; CVD, cardiovascular disease; HR, Hazard Ratio.

Supplementary Table 1. Hazard ratios and 95% confidence intervals for all coefficients in models of all-cause mortality risk among individuals with diabetes in the National Health Interview Survey, 2000 to 2014.

	All Waves HR (95% CI)	Waves ≤ 2010 HR (95% CI)	Waves > 2010 HR (95% CI)
CRN	**1.182 (1.092 - 1.280)**	**1.223 (1.112 - 1.345)**	0.967 (0.797 - 1.173)
Some College	0.955 (0.902 - 1.011)	0.940 (0.876 - 1.009)	0.884 (0.754 - 1.035)
College Degree	**0.806 (0.745 - 0.872)**	**0.785 (0.712 - 0.866)**	**0.699 (0.559 - 0.874)**
Age	**1.061 (1.059 - 1.064)**	**1.062 (1.059 - 1.065)**	**1.064 (1.056 - 1.073)**
$20,000 to < $45,000	**0.904 (0.848 - 0.962)**	**0.919 (0.854 - 0.989)**	1.106 (0.937 - 1.306)
$45,000 to < $65,000	**0.763 (0.710 - 0.820)**	**0.792 (0.725 - 0.865)**	**1.005 (0.841 - 1.202)**
$65,000 to < $85,000	**0.646 (0.585 - 0.713)**	**0.662 (0.589 - 0.743)**	0.987 (0.754 - 1.292)
$85,000 to < $100,000	**0.446 (0.336 - 0.591)**	**0.446 (0.280 - 0.710)**	**0.633 (0.428 - 0.935)**
$100,000 or more	**0.611 (0.505 - 0.739)**	**0.549 (0.406 - 0.743)**	0.859 (0.627 - 1.176)
Female Sex	**0.696 (0.663 - 0.729)**	**0.705 (0.665 - 0.747)**	**0.729 (0.645 - 0.825)**
Public Insurance	**1.434 (1.257 - 1.634)**	**1.512 (1.298 - 1.760)**	**1.529 (1.100 - 2.125)**
Private Insurance	1.014 (0.897 - 1.147)	1.019 (0.883 - 1.175)	0.949 (0.683 - 1.320)
Military	**1.212 (1.031 - 1.425)**	**1.258 (1.034 - 1.530)**	1.161 (0.774 - 1.743)
Medicare	**1.156 (1.014 - 1.317)**	**1.181 (1.016 - 1.372)**	1.247 (0.881 - 1.766)
Other	1.048 (0.740 - 1.485)	1.257 (0.883 - 1.790)	0.931 (0.116 - 7.456)
Black	**0.906 (0.851 - 0.965)**	**0.911 (0.845 - 0.981)**	0.906 (0.777 - 1.055)
Hispanic	**0.673 (0.621 - 0.729)**	**0.673 (0.615 - 0.736)**	**0.708 (0.583 - 0.859)**
American Indian/Alaskan Native	1.017 (0.807 - 1.282)	0.873 (0.659 - 1.157)	1.009 (0.565 - 1.801)
Asian	**0.537 (0.458 - 0.630)**	**0.522 (0.429 - 0.636)**	**0.585 (0.410 - 0.835)**
Other	0.822 (0.478 - 1.411)	0.721 (0.396 - 1.314)	0.467 (0.131 - 1.670)
Cancer	**1.276 (1.200 - 1.357)**	**1.471 (1.361 - 1.589)**	**1.348 (1.164 - 1.560)**
CVD, including Hypertension	**1.406 (1.318 - 1.500)**	**1.266 (1.177 - 1.361)**	1.164 (0.959 - 1.413)

Supplementary Table 2. Hazard ratios and 95% confidence intervals for all coefficients in models of all-cause mortality risk among individuals with cardiovascular disease, not including hypertension, in the National Health Interview Survey, 2000 to 2014.

	All Waves HR (95% CI)	Waves ≤ 2010 HR (95% CI)	Waves > 2010 HR (95% CI)
CRN	**1.148 (1.073 - 1.228)**	**1.180 (1.096 - 1.271)**	1.019 (0.868 - 1.195)
Some College	**0.870 (0.831 - 0.911)**	**0.870 (0.828 - 0.914)**	0.887 (0.784 - 1.003)
College Degree	**0.718 (0.677 - 0.762)**	**0.713 (0.668 - 0.761)**	**0.751 (0.646 - 0.873)**
Age	**1.074 (1.072 - 1.077)**	**1.075 (1.072 - 1.077)**	**1.071 (1.064 - 1.078)**
$20,000 to < $45,000	**0.927 (0.882 - 0.975)**	**0.911 (0.865 - 0.960)**	1.049 (0.919 - 1.198)
$45,000 to < $65,000	**0.820 (0.773 - 0.870)**	**0.813 (0.761 - 0.867)**	0.895 (0.773 - 1.036)
$65,000 to < $85,000	**0.719 (0.664 - 0.779)**	**0.720 (0.663 - 0.782)**	**0.722 (0.571 - 0.912)**
$85,000 to < $100,000	**0.613 (0.504 - 0.745)**	**0.584 (0.445 - 0.767)**	**0.700 (0.509 - 0.964)**
$100,000 or more	**0.663 (0.573 - 0.766)**	**0.586 (0.462 - 0.742)**	0.797 (0.635 - 1.001)
Female Sex	**0.718 (0.692 - 0.746)**	**0.719 (0.690 - 0.750)**	**0.714 (0.649 - 0.786)**
Public Insurance	**1.369 (1.205 - 1.555)**	**1.352 (1.181 - 1.548)**	**1.465 (1.069 - 2.008)**
Private Insurance	0.936 (0.828 - 1.059)	0.955 (0.837 - 1.088)	0.836 (0.607 - 1.152)
Military	1.065 (0.910 - 1.246)	1.084 (0.916 - 1.283)	0.985 (0.682 - 1.422)
Medicare	1.055 (0.929 - 1.199)	1.050 (0.916 - 1.203)	1.089 (0.790 - 1.500)
Other	0.653 (0.395 - 1.079)	0.672 (0.402 - 1.121)	0.416 (0.056 - 3.068)
Black	1.015 (0.954 - 1.079)	1.023 (0.957 - 1.095)	0.982 (0.848 - 1.138)
Hispanic	**0.718 (0.656 - 0.787)**	**0.711 (0.642 - 0.786)**	**0.762 (0.630 - 0.922)**
American Indian/Alaskan Native	1.081 (0.833 - 1.403)	1.128 (0.854 - 1.489)	0.793 (0.401 - 1.568)
Asian	**0.644 (0.549 - 0.756)**	**0.645 (0.539 - 0.773)**	**0.637 (0.439 - 0.924)**
Other	0.710 (0.418 - 1.207)	0.612 (0.326 - 1.149)	1.218 (0.437 - 3.394)
Diabetes	**1.466 (1.407 - 1.527)**	**1.510 (1.443 - 1.580)**	**1.273 (1.149 - 1.410)**
Cancer	**1.120 (1.076 - 1.165)**	**1.114 (1.068 - 1.163)**	**1.222 (1.095 - 1.364)**
Hypertension	**1.221 (1.167 - 1.278)**	**1.221 (1.162 - 1.284)**	**1.163 (1.036 - 1.305)**

Supplementary Table 3. Hazard ratios and 95% confidence intervals for all coefficients in models of all-cause mortality risk among individuals with cardiovascular disease, including hypertension, in the National Health Interview Survey, 2000 to 2014.

	All Waves HR (95% CI)	Waves ≤ 2010 HR (95% CI)	Waves > 2010 HR (95% CI)
CRN	**1.230 (1.163 - 1.300)**	**1.265 (1.190 - 1.346)**	1.083 (0.940 - 1.248)
Some College	**0.887 (0.856 - 0.918)**	**0.897 (0.864 - 0.932)**	**0.834 (0.756 - 0.919)**
College Degree	**0.752 (0.718 - 0.787)**	**0.759 (0.722 - 0.798)**	**0.718 (0.634 - 0.813)**
Age	**1.077 (1.076 - 1.079)**	**1.078 (1.076 - 1.080)**	**1.075 (1.069 - 1.080)**
$20,000 to < $45,000	**0.886 (0.854 - 0.919)**	**0.874 (0.841 - 0.907)**	0.989 (0.893 - 1.095)
$45,000 to < $65,000	**0.795 (0.760 - 0.832)**	**0.782 (0.745 - 0.820)**	0.904 (0.802 - 1.017)
$65,000 to < $85,000	**0.662 (0.623 - 0.702)**	**0.656 (0.616 - 0.698)**	**0.706 (0.592 - 0.841)**
$85,000 to < $100,000	**0.588 (0.509 - 0.678)**	**0.558 (0.456 - 0.682)**	**0.686 (0.541 - 0.870)**
$100,000 or more	**0.621 (0.562 - 0.687)**	**0.600 (0.516 - 0.697)**	**0.707 (0.586 - 0.851)**
Female Sex	**0.663 (0.644 - 0.682)**	**0.663 (0.642 - 0.684)**	**0.661 (0.614 - 0.711)**
Public Insurance	**1.299 (1.197 - 1.411)**	**1.303 (1.192 - 1.423)**	**1.297 (1.056 - 1.594)**
Private Insurance	**0.852 (0.788 - 0.920)**	**0.871 (0.803 - 0.946)**	**0.745 (0.607 - 0.913)**
Military	1.036 (0.935 - 1.149)	1.047 (0.936 - 1.170)	0.975 (0.762 - 1.248)
Medicare	0.956 (0.882 - 1.036)	0.960 (0.880 - 1.046)	0.939 (0.760 - 1.160)
Other	0.821 (0.603 - 1.118)	0.839 (0.610 - 1.154)	0.595 (0.154 - 2.304)
Black	0.971 (0.930 - 1.014)	0.981 (0.936 - 1.029)	0.914 (0.816 - 1.024)
Hispanic	**0.705 (0.662 - 0.751)**	**0.700 (0.654 - 0.749)**	**0.737 (0.637 - 0.853)**
American Indian/Alaskan Native	1.189 (0.975 - 1.450)	**1.230 (1.006 - 1.505)**	0.955 (0.584 - 1.562)
Asian	**0.659 (0.582 - 0.747)**	**0.666 (0.578 - 0.768)**	**0.639 (0.506 - 0.808)**
Other	0.766 (0.503 - 1.166)	0.743 (0.463 - 1.192)	0.937 (0.398 - 2.206)
Diabetes	**1.482 (1.434 - 1.531)**	**1.514 (1.461 - 1.568)**	**1.328 (1.225 - 1.439)**
Cancer	**1.306 (1.261 - 1.351)**	**1.299 (1.251 - 1.349)**	**1.346 (1.233 - 1.469)**

Supplementary Table 4. Hazard ratios and 95% confidence intervals for all coefficients in models of diabetes-specific mortality risk among individuals with diabetes in the National Health Interview Survey, 2000 to 2014.

	All Waves HR (95% CI)	Waves ≤ 2010 HR (95% CI)	Waves > 2010 HR (95% CI)
CRN	**1.226 (1.074 - 1.399)**	**1.289 (1.111 - 1.496)**	1.055 (0.779 - 1.430)
Some College	0.956 (0.856 - 1.069)	0.972 (0.860 - 1.100)	0.911 (0.691 - 1.201)
College Degree	**0.819 (0.702 - 0.956)**	**0.835 (0.707 - 0.987)**	0.780 (0.525 - 1.158)
Age	**1.068 (1.063 - 1.073)**	**1.070 (1.064 - 1.075)**	**1.061 (1.048 - 1.075)**
$20,000 to < $45,000	0.910 (0.810 - 1.022)	0.902 (0.794 - 1.025)	1.066 (0.795 - 1.429)
$45,000 to < $65,000	**0.765 (0.671 - 0.872)**	**0.746 (0.644 - 0.865)**	1.003 (0.719 - 1.400)
$65,000 to < $85,000	**0.685 (0.576 - 0.815)**	**0.639 (0.531 - 0.770)**	1.186 (0.728 - 1.932)
$85,000 to < $100,000	**0.423 (0.250 - 0.714)**	**0.339 (0.149 - 0.773)**	0.697 (0.346 - 1.402)
$100,000 or more	**0.473 (0.322 - 0.696)**	**0.465 (0.260 - 0.832)**	0.627 (0.349 - 1.128)
Female Sex	**0.689 (0.631 - 0.752)**	**0.687 (0.623 - 0.756)**	**0.690 (0.565 - 0.843)**
Public Insurance	**1.671 (1.318 - 2.119)**	**1.625 (1.256 - 2.102)**	**2.245 (1.254 - 4.022)**
Private Insurance	1.098 (0.882 - 1.367)	1.043 (0.823 - 1.321)	1.491 (0.829 - 2.684)
Military	**1.417 (1.052 - 1.907)**	**1.380 (1.003 - 1.899)**	1.856 (0.923 - 3.734)
Medicare	1.243 (0.982 - 1.572)	1.171 (0.909 - 1.508)	1.817 (0.981 - 3.364)
Other	**1.895 (1.059 - 3.392)**	**1.904 (1.059 - 3.423)**	0.240 (0.026 - 2.221)
Black	0.975 (0.865 - 1.099)	0.972 (0.856 - 1.104)	0.972 (0.712 - 1.328)
Hispanic	**0.662 (0.577 - 0.760)**	**0.621 (0.531 - 0.727)**	0.891 (0.649 - 1.224)
American Indian/Alaskan Native	0.840 (0.539 - 1.307)	0.802 (0.495 - 1.299)	1.125 (0.456 - 2.778)
Asian	**0.523 (0.377 - 0.724)**	**0.494 (0.343 - 0.712)**	0.669 (0.340 - 1.316)
Other	0.315 (0.099 - 1.003)	0.375 (0.115 - 1.223)	0.957 (0.443 - 2.070)

Supplementary Table 5. Hazard ratios and 95% confidence intervals for all coefficients in models of cardiovascular disease-specific mortality risk among individuals with cardiovascular disease in the National Health Interview Survey, 2000 to 2014.

	All Waves HR (95% CI)	Waves ≤ 2010 HR (95% CI)	Waves > 2010 HR (95% CI)
CRN	1.123 (0.993 - 1.271)	**1.172 (1.028 - 1.337)**	1.054 (0.757 - 1.468)
Some College	**0.866 (0.797 - 0.940)**	**0.870 (0.796 - 0.950)**	0.910 (0.720 - 1.150)
College Degree	**0.649 (0.580 - 0.726)**	**0.645 (0.570 - 0.729)**	**0.699 (0.509 - 0.961)**
Age	**1.094 (1.090 - 1.098)**	**1.095 (1.091 - 1.100)**	**1.090 (1.078 - 1.102)**
$20,000 to < $45,000	**0.888 (0.813 - 0.971)**	**0.876 (0.798 - 0.963)**	1.217 (0.943 - 1.570)
$45,000 to < $65,000	**0.806 (0.728 - 0.892)**	**0.818 (0.734 - 0.913)**	1.003 (0.749 - 1.345)
$65,000 to < $85,000	**0.700 (0.610 - 0.803)**	**0.710 (0.613 - 0.823)**	0.725 (0.472 - 1.113)
$85,000 to < $100,000	**0.560 (0.392 - 0.802)**	**0.540 (0.339 - 0.862)**	0.943 (0.526 - 1.691)
$100,000 or more	**0.432 (0.310 - 0.601)**	**0.356 (0.219 - 0.578)**	0.829 (0.524 - 1.311)
Female Sex	**0.625 (0.582 - 0.670)**	**0.631 (0.586 - 0.681)**	**0.583 (0.476 - 0.715)**
Public Insurance	1.058 (0.849 - 1.318)	1.040 (0.820 - 1.318)	1.145 (0.614 - 2.135)
Private Insurance	**0.799 (0.644 - 0.990)**	**0.791 (0.631 - 0.992)**	0.675 (0.354 - 1.289)
Military	0.805 (0.610 - 1.063)	0.858 (0.643 - 1.145)	0.571 (0.246 - 1.326)
Medicare	0.834 (0.668 - 1.042)	0.837 (0.660 - 1.060)	0.770 (0.400 - 1.481)
Other	1.205 (0.603 - 2.408)	1.173 (0.574 - 2.397)	1.443 (0.173 - 12.037)
Black	**1.225 (1.095 - 1.371)**	**1.253 (1.109 - 1.416)**	1.093 (0.794 - 1.505)
Hispanic	**0.789 (0.677 - 0.919)**	**0.788 (0.666 - 0.931)**	0.814 (0.571 - 1.159)
American Indian/Alaskan Native	1.386 (0.799 - 2.402)	1.477 (0.824 - 2.646)	0.817 (0.180 - 3.711)
Asian	**0.667 (0.505 - 0.880)**	**0.734 (0.545 - 0.989)**	0.443 (0.181 - 1.083)
Other	0.962 (0.372 - 2.491)	0.610 (0.229 - 1.622)	3.306 (0.703 - 15.545)

Supplementary Table 6. Hazard ratios and 95% confidence intervals for all coefficients in models of cardiovascular disease or hypertension mortality risk among individuals with cardiovascular disease or hypertension in the National Health Interview Survey, 2000 to 2014.

	All Waves HR (95% CI)	Waves ≤ 2010 HR (95% CI)	Waves > 2010 HR (95% CI)
CRN	**1.300 (1.187 - 1.424)**	**1.326 (1.198 - 1.467)**	**1.311 (1.051 - 1.634)**
Some College	**0.910 (0.859 - 0.964)**	**0.926 (0.870 - 0.985)**	0.852 (0.717 - 1.011)
College Degree	**0.738 (0.683 - 0.797)**	**0.758 (0.696 - 0.826)**	**0.643 (0.521 - 0.794)**
Age	**1.097 (1.094 - 1.100)**	**1.098 (1.094 - 1.101)**	**1.096 (1.088 - 1.105)**
$20,000 to < $45,000	**0.850 (0.798 - 0.905)**	**0.840 (0.786 - 0.898)**	1.039 (0.883 - 1.224)
$45,000 to < $65,000	**0.790 (0.735 - 0.849)**	**0.783 (0.726 - 0.845)**	0.998 (0.824 - 1.209)
$65,000 to < $85,000	**0.614 (0.555 - 0.679)**	**0.610 (0.548 - 0.679)**	**0.700 (0.520 - 0.942)**
$85,000 to < $100,000	**0.469 (0.359 - 0.613)**	**0.426 (0.304 - 0.598)**	0.753 (0.490 - 1.158)
$100,000 or more	**0.438 (0.355 - 0.539)**	**0.383 (0.287 - 0.511)**	0.732 (0.523 - 1.024)
Female Sex	**0.601 (0.572 - 0.631)**	**0.606 (0.575 - 0.639)**	**0.567 (0.494 - 0.650)**
Public Insurance	**1.188 (1.028 - 1.373)**	1.165 (0.995 - 1.364)	1.358 (0.948 - 1.947)
Private Insurance	**0.788 (0.686 - 0.905)**	**0.769 (0.661 - 0.893)**	0.809 (0.572 - 1.143)
Military	0.960 (0.798 - 1.153)	0.960 (0.790 - 1.168)	0.984 (0.624 - 1.554)
Medicare	**0.843 (0.730 - 0.974)**	**0.832 (0.712 - 0.973)**	0.882 (0.602 - 1.294)
Other	0.783 (0.486 - 1.261)	0.751 (0.460 - 1.226)	0.911 (0.201 - 4.124)
Black	**1.155 (1.078 - 1.237)**	**1.164 (1.083 - 1.252)**	1.108 (0.916 - 1.341)
Hispanic	**0.777 (0.707 - 0.854)**	**0.754 (0.679 - 0.836)**	0.955 (0.768 - 1.188)
American Indian/Alaskan Native	1.331 (0.910 - 1.947)	1.417 (0.967 - 2.076)	0.737 (0.281 - 1.934)
Asian	**0.720 (0.605 - 0.857)**	**0.742 (0.609 - 0.903)**	**0.676 (0.456 - 1.000)**
Other	0.675 (0.369 - 1.235)	**0.416 (0.203 - 0.851)**	2.593 (0.996 - 6.751)

Supplementary Table 7. Association of CRN and all-cause and disease-specific mortality among National Health Interview Survey (2000- 2014) participants with diabetes, cardiovascular disease, and/or hypertension after excluding potentially influential cases.

|	Follow-Up Time, Weeks Median (IQR)	All-Cause Mortality			Disease Specific Mortality		
		Died: N (%)	Model 1: HR (95% CI)[1]	Model 2: HR (95% CI)[2]	Died: N (%)	Model 1: HR (95% CI)[1]	Model 2: HR (95% CI)[3]
Full Sample							
CRN for Diabetes	295 (161 - 504)	8737 (23.5)	**0.748 (0.686 - 0.815)**	**1.182 (1.091 - 1.280)**	2882 (8.4)	**0.750 (0.669 - 0.840)**	**1.180 (1.045 - 1.331)**
CRN for CVD, narrow definition*	313 (165 - 539)	15979 (27.6)	**0.646 (0.600 - 0.694)**	**1.133 (1.066 - 1.205)**	4692 (8.9)	**0.602 (0.542 - 0.668)**	1.080 (0.968 - 1.206)
CRN for CVD, expanded definition**	326 (178 - 561)	28340 (19.4)	**0.705 (0.667 - 0.746)**	**1.232 (1.172 - 1.296)**	10028 (7.39)	**0.695 (0.643 - 0.752)**	**1.265 (1.162 - 1.378)**
2000-2010 Waves							
CRN for Diabetes	456 (321 - 613)	7650 (31.9)	**0.799 (0.240 - 0.862)**	**1.225 (1.125 - 1.334)**	2258 (10.39)	**0.765 (0.676 - 0.867)**	**1.210 (1.061 - 1.380)**
CRN for CVD, narrow definition*	478 (322 - 635)	14146 (35.4)	**0.706 (0.664 - 0.750)**	**1.151 (1.079 - 1.228)**	4692 (12.0)	**0.631 (0.656 - 0.704)**	**1.125 (1.003 - 1.262)**
CRN for CVD, expanded definition**	500 (339 - 648)	25180 (25.5)	**0.774 (0.737 - 0.813)**	**1.244 (1.180 - 1.310)**	9143 (9.9)	**0.724 (0.667 - 0.786)**	**1.309 (1.197 - 1.432)**
2011 - 2014 Waves							
CRN for Diabetes	152 (100 - 204)	1092 (8.2)	**0.610 (0.505 - 0.737)**	1.000 (0.818 - 1.225)	324 (2.6)	**0.706 (0.521 - 0.958)**	1.103 (0.795 - 1.532)
CRN for CVD, narrow definition*	156 (100 - 208)	1833 (10.2)	**0.554 (0.473 - 0.647)**	1.031 (0.877 - 1.211)	380 (2.3)	**0.494 (0.359 - 0.679)**	0.993 (0.701 - 1.406)
CRN for CVD, expanded definition**	156 (104 - 208)	3043 (6.5)	**0.584 (0.511 - 0.670)**	1.061 (0.927 - 1.214)	885 (2.0)	**0.569 (0.457 - 0.709)**	1.096 (0.864 - 1.390)

Note: All hazard ratios are weighted for survey design. Disease specific mortality is defined as having a listed cause of death of diabetes, heart or cerebrovascular disease, or heart, cerebrovascular disease or underlying hypertension for diabetes, CVD, and CVD with hypertension models, respectively. Bold face denotes statistical significance. *The narrow definition of CVD includes heart attack, angina pectoris, coronary heart disease, other heart condition, or stroke. ** The expanded definition of CVD includes all conditions for the narrow definition or a diagnosis of hypertension. 1. Unadjusted Hazard Ratio. 2. Hazard Ratio 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). 3. Hazard ratio adjusted for age, sex, insurance (private, public, Medicare, other, or none), race (white, Black or African American, Hispanic or Latino, Asian, or other), and education (≤ high school, some college, college degree or greater). Abbreviations: CRN, cost-related nonadherence; CVD, cardiovascular disease; HR, Hazard Ratio.

Supplementary Table 8. Association of CRN and all-cause and disease-specific mortality among National Health Interview Survey (2000- 2014) participants with diabetes, cardiovascular disease, and/or hypertension after adjusting for age using natural splines at age 75.

	Follow-Up Time, Weeks Median (IQR)	All-Cause Mortality			Disease-Specific Mortality		
		Died: N(%)	Model 1: HR (95% CI)	Model 2: HR (95% CI)	Died: N(%)	Model 1: HR (95% CI)	Model 2: HR (95% CI)
Full Sample							
CRN for Diabetes	291 (156 - 504)	8909 (23.6)	**0.752 (0.694 - 0.815)**	**1.158 (1.063 - 1.261)**	3045 (8.7)	**0.766 (0.674 - 0.870)**	**1.228 (1.076 - 1.402)**
CRN for CVD, narrow definition*	304 (160 - 534)	16345 (27.8)	**0.702 (0.658 - 0.750)**	**1.147 (1.072 - 1.228)**	4845 (9.1)	**0.618 (0.548 - 0.696)**	1.119 (0.989 - 1.267)
CRN for CVD, expanded definition**	322 (169 - 552)	28755 (19.5)	**0.771 (0.732 - 0.813)**	**1.229 (1.162 - 1.300)**	10321 (7.4)	**0.728 (0.669 - 0.792)**	**1.300 (1.183 - 1.421)**
2000-2010 Waves							
CRN for Diabetes	465 (360 - 652)	7379 (34.1)	**0.799 (0.731 - 0.875)**	**1.220 (1.109 - 1.343)**	2563 (13.0)	**0.809 (0.700 - 0.934)**	**1.288 (1.111 - 1.496)**
CRN for CVD, narrow definition*	474 (330 - 630)	13771 (37.4)	**0.734 (0.685 - 0.786)**	**1.180 (1.095 - 1.271)**	4282 (12.9)	**0.659 (0.582 - 0.747)**	**1.170 (1.025 - 1.335)**
CRN for CVD, expanded definition**	508 (360 - 652)	24440 (27.1)	**0.805 (0.760 - 0.852)**	**1.264 (1.188 - 1.344)**	9023 (10.7)	**0.758 (0.691 - 0.833)**	**1.322 (1.194 - 1.464)**
2011 - 2014 Waves							
CRN for Diabetes	165 (104 - 230)	1530 (9.5)	**0.681 (0.605 - 0.767)**	0.960 (0.790 - 1.166)	482 (3.2)	**0.779 (0.639 - 0.950)**	1.055 (0.777 - 1.434)
CRN for CVD, narrow definition*	161 (100 - 230)	2574 (11.8)	**0.620 (0.562 - 0.684)**	1.007 (0.856 - 1.183)	563 (2.8)	**0.768 (0.633 - 0.931)**	1.042 (0.747 - 1.453)
CRN for CVD, expanded definition**	165 (104 - 234)	4315 (7.5)	**0.695 (0.643 - 0.752)**	1.076 (0.932 - 1.241)	1298 (2.4)	**0.802 (0.700 - 0.918)**	**1.201 (1.042 - 1.623)**

Note: All hazard ratios are weighted for survey design. Disease specific mortality is defined as having a listed cause of death of diabetes, heart or cerebrovascular disease, or heart, cerebrovascular disease or underlying hypertension for diabetes, CVD, and CVD with hypertension models, respectively. Bold face denotes statistical significance. *The narrow definition of CVD includes heart attack, angina pectoris, coronary heart disease, other heart condition, or stroke. ** The expanded definition of CVD includes all conditions for the narrow definition or a diagnosis of hypertension. 1. Unadjusted Hazard Ratio. 2. Hazard Ratio 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). 3. Hazard ratio adjusted for age, sex, insurance (private, public, Medicare, other, or none), race (white, Black or African American, Hispanic or Latino, Asian, or other), and education (≤ high school, some college, college degree or greater). Abbreviations: CRN, cost-related nonadherence; CVD, cardiovascular disease; HR, Hazard Ratio.

Supplementary Figure 1. Directed acyclic graph depicting hypothesized causal interrelations between CRN, sociodemographic characteristics, and all-cause mortality.
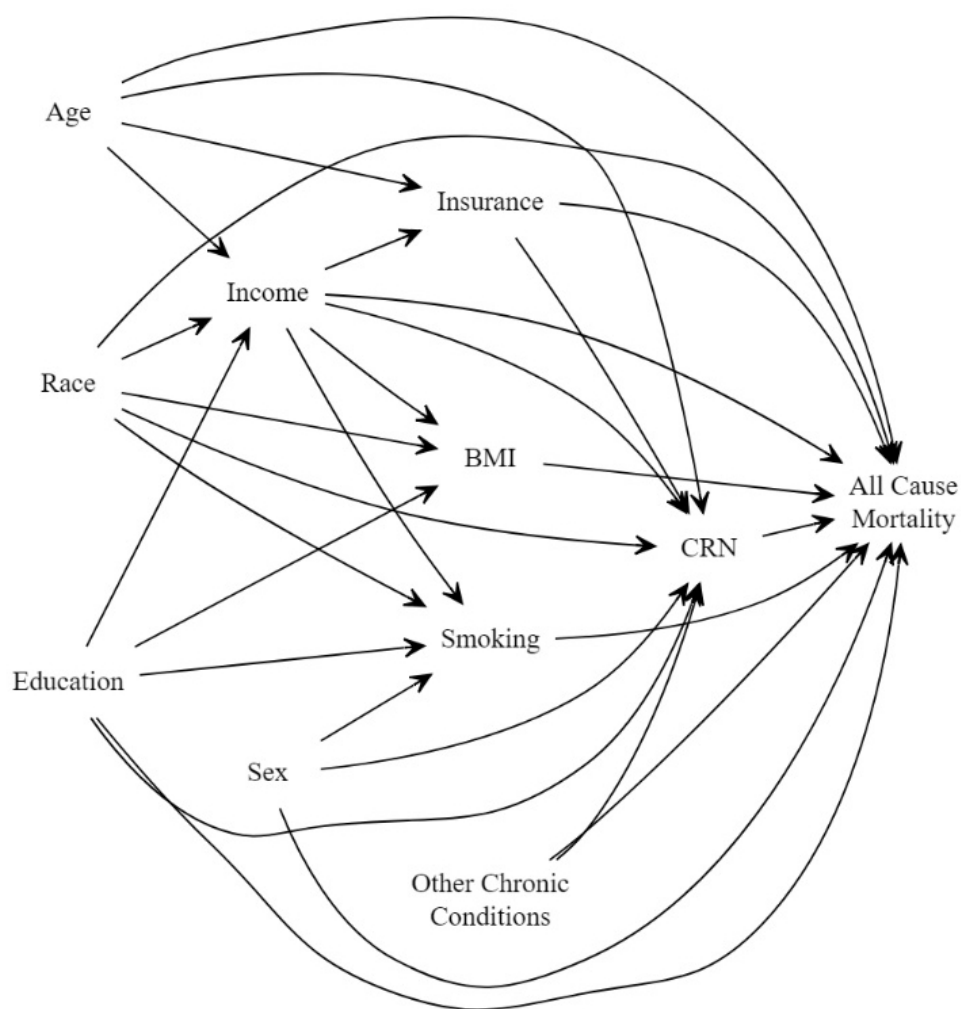
Supplementary Figure 2. Directed acyclic graph depicting hypothesized causal interrelations between CRN, sociodemographic characteristics, and disease-specific mortality.