***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 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 data from the National Health Interview Survey (NHIS). 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.32 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 varied 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.32 Questions relating to CRN were introduced into the survey in 2000, thus, the current study included only the 2000-2014 waves.

*Study Sample*

Only individuals age 18 and over with diabetes, hypertension, and/or CVD were included in 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). CVD was operationalized 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. An alternate classification of CVD that included a diagnosis of hypertension (*N* = 133,967) was also considered, yielding a total of 156,892 participants with CVD.

**Measures**

*Primary Exposure*

The primary exposure was CRN. Because CRN was assessed differently in the NHIS before and after 2010, data were harmonized to generate a single dichotomous variable representing whether a participant had experienced CRN in the previous year. From 2000 to 2009, CRN was operationalized 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 specific CRN behaviors, thus CRN was operationalized 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.33

*Outcome Measures*

The two primary outcomes for the secondary data 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 or providing insufficient identifying information were not eligible for linkage. Given that ineligible individuals may differ systematically from those who are eligible, mortality specific weights were assigned to eligible participants to correct for possible selection bias. Further, as the public use data provides only year and quarter of death rather than exact dates, follow-up time was calculated as the date of interview to the last day in the quarter and year of death, when vital status was ascertained. Follow-up time was censored at December 31, 2015 for surviving individuals. Ten participants with diabetes (0.0007 %) and eight participants with heart conditions or CVD (0.0003 %) were excluded from analyses because recorded death dates occurred prior to interview dates.

*All-cause mortality*

All participants with positive linkage to the NDI were considered as having the outcome of all-cause mortality.

*Disease-specific mortality*

Probabilistic linkage between participant records and the NDI 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. Disease-specific deaths due to diabetes included those in which diabetes was listed as the primary cause of death and those in which diabetes (ICD-10 codes E10 – E14) was flagged as a contributing cause of death by probabilistic matches of NHIS participant records to the NDI. Two definitions of disease-specific deaths were included for individuals with CVD, depending upon whether the definition of CVD was expanded to include hypertension. For the narrower definition, disease-specific deaths due to CVD included 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, disease-specific deaths included all causes listed in the narrow definition as well as essential hypertension and hypertensive renal disease (ICD-10 codes I10, I12, and I15). Disease-specific mortality was considered 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 models where the listed cause of death matched the disease of interest. For example, if an individual with both diabetes and CVD was listed as having diabetes as their primary cause of death, they were considered to have disease-specific mortality in diabetes models but not in CVD models.

*Statistical Analyses*

Cox proportional hazard regressions for diabetes and CVD were used to assess the associations between CRN and risks of all-cause and disease-specific mortality. Two definitions of CVD were modelled: one, stroke or any heart condition, excluding hypertension, and two, stroke or any heart condition, including hypertension. For disease-specific mortality, Model 1 included only CRN and Model 2 was 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). For all-cause mortality, Model 1 included only CRN, while Model 2 included all adjustment variables for disease-specific mortality as well as diagnosis of cancer (for all models), diabetes (for CVD models), hypertension (for diabetes and CVD models not including hypertension) and CVD (for diabetes models). Adjustment variables were selected according to a directed acyclic graphs (DAGs) as the minimally sufficient sets to block all backdoor pathways between CRN and mortality (Supplemental Figure 1). As all included variables had fewer than 1% missing information, cases with missing data were deleted listwise. Models were also stratified by year of interview (≤ 2009, > 2009) as a sensitivity analysis to determine if the change in measurement of CRN in 2010 substantially impacted findings. All analyses were conducted in R, version 3.6.1.34 To account for the complex sampling methodology of the NHIS, all regressions and descriptive statistics accounted for survey design using the *survey* package35 in R.

**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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|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | 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. | | | | | | | |  |  |