***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 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 cardiovascular disease are associated with significant economic burden. Together, diabetes and cardiovascular disease 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, cardiovascular disease, 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 heart disease 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 cardiovascular disease.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, cardiovascular disease, and/or hypertension and b) to determine whether CRN is associated with higher risk of mortality in U.S. adults with diabetes, cardiovascular disease, and/or hypertension.

**Approach**

*Study Sample*

Data were taken 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 All interviews were conducted using computer-assisted personal interviews by trained U.S. Census Bureau staff, and consist of two parts: 1) the ‘core’ questionnaire and 2) supplemental questions. The core questionnaire consists of four subsections (Household, Family, Sample Adult, and Sample Child) which broadly assess 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.32 Questions relating to CRN were introduced into the survey in 2000, hence the current study focuses on the 2000-2014 waves only.

The present analyses include only individuals age 18 with diabetes and/or cardiovascular disease. 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* = 13,367). Cardiovascular disease included a diagnosis of one or more of the following: “a heart attack (sometimes called myocardial infarction?” (*N* = 5,312), “angina pectoris?” (*N* = 3,683), “coronary heart disease (CHD)?” (*N* = 8,537), or “any kind of heart condition other than coronary heart disease, angina pectoris, or a heart attack?” (*N* = 13,095) or “any kind of stroke?” (*N* = 5,264). In total, there were 18,329 with CVD. Alternate classifications of heart disease and CVD that included a diagnosis of hypertension (*N* = 45,587) were also considered, yielding a total of 47,828 participants with CVD.

*Primary Exposure*

The primary exposure was CRN, treated as a binary variable. From 2000 to 2009, CRN was assessed by a single item asking whether participants had needed, but couldn’t afford, medication in the previous year. Alternate questions regarding specific CRN behaviors were introduced in 2010; thus, from 2010 to 2014 CRN was defined 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*

The two primary outcomes were all-cause and disease-specific mortality (i.e. diabetes, disease of heart, or cerebrovascular disease). Vital status through 2015 was determined through linkage to the National Death Index. Participants younger than age 18 and respondents providing insufficient identifying information for were not eligible for linkage. Mortality specific weights were assigned to eligible participants to correct for possible selection bias, as ineligible individuals may differ systematically from those who are eligible. The public use data provides only year and quarter of death rather than exact dates, so 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. 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.

*Statistical Analyses*

Individual Cox regressions for each chronic condition were used to assess the risks of all-cause and disease-specific mortality associated with CRN. Model 1 included only CRN, while Model 2 was adjusted for age, race (White, Black, Asian, Hispanic, or other), region (South, Midwest, Northeast, or West), household income, insurance (private, public, Medicare, other, or none), smoking status (never, former, or current), and body mass index (. A sensitivity analysis excluding participants interviewed after 2009 was also conducted 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 were adjusted 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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