***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 heart disease are the two most expensive conditions for patients in the U.S. healthcare system. Together, these diseases accounted for nearly $200 billion in personal healthcare spending in 2013, a figure which rises to $280 billion when accounting for treatment of hypertension, a condition commonly comorbid with diabetes and heart disease.1,2 Prescription drug costs accounted for 57.6%, 11.3%, and 41.2% of total diabetes, heart disease, and hypertension costs, respectively, and have continued to increase at an average rate of 5-6% annually.1

To cope with steadily rising prices, patients with chronic illness may adopt behaviors such as skipping, delaying, or rationing medication. These behaviors, collectively referred to as cost-related nonadherence (CRN), are reported as the sole or primary reason for nonadherence in two-thirds of nonadherent patients with chronic illness, making them the most common form of treatment non-compliance.3 Sixteen to 20% of patients with diabetes, hypertension, or heart disease reported CRN in 2004,4 and limited data suggest that these numbers have since increased. Two small 2018 surveys of U.S. adults with diabetes each reported that 25% of respondents had rationed insulin in the previous year to manage costs, with 3.2% doing so on a daily basis, 38.6% decreasing use of blood glucose testing, and 40% failing to discuss underuse with their physician.5,6

Despite the prevalence, there is limited research on clinical outcomes of CRN. Several clinical trials have found that providing patients with free access to medication, and thus eliminating CRN, decreases risk of adverse outcomes such as stroke and revascularization7 and improves indicators such as hemoglobin A1c, LDL cholesterol, and diastolic blood pressure,8 although neither found significant reductions in mortality after 1-year of follow-up. Further, overall adherence in the intervention arms of both trials was low (~30%), and given that nonadherence in general is associated with increased risk of all-cause mortality and other adverse outcomes in patients with diabetes and heart disease,9–12 the null findings may be a consequence of low treatment uptake. The objectives of this study are a) to assess the prevalence of CRN in a representative sample of U.S. adults with diabetes, heart disease, and/or hypertension and b) to determine whether CRN increases the risk of mortality in U.S. adults with diabetes, heart disease, and/or hypertension using a longer follow-up period to overcome some of the limitations of previous trials.

**Approach**

*Study Sample*

Data will be 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.13 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.13 Questions relating to CRN were introduced into the survey in 2010; thus, the current study will focus on the 2010-2014 waves only.

The present analyses will include only individuals age 18 and over who responded affirmatively that they had been told by a doctor or health professional that they had: “(Other than during pregnancy) diabetes or sugar diabetes?” (*N* = 13,367), “hypertension, also called high blood pressure?” (*N* = 45,587), “a heart attack (sometimes called myocardial infarction?” (*N* = 51,312), “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). Heart-related conditions will be further grouped into any kind of heart disease (CHD, heart attack, angina pectoris, other; *N* = 20,738) and any kind of cardiovascular disease (CVD) (any heart disease, stroke; *N* = 23,468).

*Variables*

The primary exposure will be CRN, assessed via three questions that ask participants whether, in order to save money, they had skipped medication doses, taken less medicine than prescribed, or delayed taking medicine in the last year. CRN may be represented as an ordinal variable corresponding to the number of cost-saving measures reported by a participant, three separate independent variables, a single independent variable representing any affirmative response, or an eight-category variable representing all possible combinations of cost-saving behaviors.

The primary outcome will be all-cause mortality, with potential sensitivity analyses for cause-specific mortality (e.g. mortality from diabetes for participants with diabetes). The vital status for each participant through 2015 will be determined through linkage to the National Death Index (NDI). Participants younger than age 18 and respondents providing insufficient identifying information are not eligible for linkage and will be excluded from analyses. Given the possibility for selection bias and systematic differences between eligible and non-eligible participants, analyses will be weighted for survey design and selection probability in mortality data. Further, the public use data provides only year and quarter of death rather than exact dates, so follow-up time will be calculated as the date of interview to the last day in the quarter and year of death. This definition of follow-up time was selected rather than using the midpoint of the quarter to minimize inconsistencies between interview and death dates. The recorded interview date for 106 individuals occurred later than the midpoint of the quarter of death; using the end of quarter as the censoring of follow-up time reduced the number of inconsistent follow-up times to 38 individuals, who will be excluded from analyses. Nonetheless, descriptive statistics comparing CRN, diabetes, and heart conditions between individuals with and without inconsistent follow-up times will be conducted to understand potential selection bias.

*Statistical Analyses*

Individual Cox proportional hazards models for each chronic condition, as well as the aggregate conditions of heart disease and CVD, will be used to assess the risk of all-cause and cause-specific mortality from CRN. Although the covariates included in models will be selected using a causal modelling strategy (i.e. Directed Acyclic Graph), generally, Model 1 will include CRN only, Model 2 will be adjusted for demographics, such as age, sex, and race, and Model 3 will be further adjusted for insurance status, comorbidities, other forms of non-adherence, and barriers to healthcare utilization. Sensitivity analyses may be conducted for robustness of findings if pre-diabetics are also included, treated CRN as a binary variable (Any CRN behavior vs. None), and for different treatments of missing data.

*Note About IRB Approval*: This project will need IRB approval, although it will be filed under exempt status because no individually identifiable information is available.

**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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