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

**INTRODUCTION AND OBJECTIVES**

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

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

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

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

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

**METHODS**

**Source Data**

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

*Study Sample*

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

**Measures**

*Primary Exposure*

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

*Outcome Measures*

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

*All-cause mortality*

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

*Disease-specific mortality*

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

*Statistical Analyses*

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

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

Additionally, we conducted a sensitivity analysis by stratifying at year of interview (≤ 2010, > 2010) to determine if the change in measurement of CRN in 2010 substantially impacted findings. We evaluated models for presence of influential observations and multicollinearity using standardized dfbeta values, and variance inflation factors, respectively, tested for proportional hazards using scaled Schoenfeld residuals,38 and assessed log-linearity of by plotting Martingale residuals against continuous predictors (i.e. age). All analyses were conducted in R, version 3.6.1.39 Additionally, to account for the complex sampling methodology of the NHIS, all regressions and descriptive statistics were adjusted for survey design using the *survey* package40 in R.

**Results**

*Descriptive Statistics*

The final analytic sample sizes were 34,839 for diabetes, 53,009 for CVD excluding and 128,723 for CVD including hypertension. Thirty-nine percent of participants with diabetes reported at least one form of CRN, as did 38.8% of participants with CVD and 34.7% 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%). Participants with CRN were significantly younger and had higher BMIs than those without CRN, and were more likely to be female, non-white, uninsured, or current smokers (all *p* < 0.001). Income and education were also significantly associated with CRN (both *p* < 0.001). 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 308 weeks (IQR = 169 – 500). As shown in Table 2, the unadjusted hazard of all-cause mortality in individuals with CRN was 0.752 times (95% CI = 0.694 – 0.815) that of those without CRN. The direction of association between CRN and all-cause mortality was reversed after adjusting for potential confounders, such that CRN was associated with an 18.3% increase in the hazard of death (95% CI = 1.092 – 1.281) in individuals with diabetes relative to those without CRN. After stratifying by interview year, we found that, among individuals with diabetes, the unadjusted association between CRN and all-cause mortality was higher and the adjusted association lower for individuals interviewed prior to 2011 relative to those interviewed in and after 2011 (unadjusted *p*interaction= 0.006; adjusted *p*interaction= 0.004, Table 2).

*Cardiovascular Disease*

The median length of follow-up for individuals with CVD, excluding hypertension, was 330 (IQR = 174 – 530). During that time, 16,345 (27.8%) of individuals categorized under the narrow definition of CVD died, 1,645 (10.1%) of whom reported CRN. CRN was associated with a 29.8% lower hazard of death (95% CI = 0.658 – 0.252) in the unadjusted model and a 14.8% increase in the hazard of death after adjustment (95% CI = 1.073 – 1.300) among individuals with CVD. The unadjusted hazard ratio of all-cause mortality for CRN was lower among those interviewed in and after 2011 compared to those interviewed before 2011 (*p*interaction < 0.001), while the adjusted hazard ratio did not significantly differ by interview period (*p*interaction = 0.149; Table 2).

*Cardiovascular Disease including Hypertension*

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

**Disease-Specific Mortality**

*Diabetes*

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

*Cardiovascular Disease*

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

*Cardiovascular Disease including Hypertension*

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

**Model Assumptions**

We identified 121, 94, and 160 cases with higher than average standardized dfbeta values on at least one variable in disease-specific diabetes, CVD, and CVD or hypertension, respectively. Similarly, 78, 153, and 123 potentially influential cases were identified in all-cause diabetes, CVD, and CVD or hypertension models. Potentially influential cases tended to have higher numbers of medical comorbidities than non-influential cases but were similar in age, race, sex, and other confounding variables. Given that exclusion of potentially influential cases did not substantially change estimates (Supplementary Table 1), we retained these cases in final models. Models did not show evidence of multicollinearity (all VIFs < 1.5). Age displayed log-linearity with estimated hazards from 18 – 75 years, after which there was a non-linear increase in the risks of both all-cause and disease specific deaths. Refitting models using natural splines at age 75 did not change results, thus we report the simpler linear effects (Supplementary Table 2.) Finally, while the assumption of proportional hazards was met for CRN associated risks in all adjusted models, all models violated the proportional hazards assumption globally (all *p* < 0.001).

**Discussion**

**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. | | | | | | | |  |  |