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Competing Risk of Death and Time-Varying Covariates in Cardiovascular Epidemiologic Research: Modeling the Hazards of Coronary Heart Disease in the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study

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Abstract

Competing risk of death and time-varying covariates, often overlooked during statistical analyses of longitudinal studies, can alter the magnitude of estimates of the effect of covariates on the hazards of health outcomes. This study aimed to investigate whether estimates obtained when modeling the effect of risk factors on the hazards of coronary heart disease (CHD) varied significantly while accounting for the presence of competing risk of death and time-varying covariates. We used data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (n=6346) to model estimates of the effect of risk factors on the hazards of CHD using Cox proportional hazards model, Cox extension with time-varying covariates, and the Fine Gray approach. We used a chi-square test to

compare coefficient estimates obtained from the three modeling techniques. We obtained a P-value > 0.05 when comparing coefficient estimates for body mass index, age, cholesterol, smoking, and diabetes after fitting the three models. Coefficient estimates obtained when modeling the effect of risk factors on the hazards of CHD did not vary significantly in the presence of competing risk of death and time-varying covariates. Researchers should consider exploring these concepts more systematically in cohort studies with cardiovascular outcomes.

Keywords

competing risk of death, coronary heart disease, Cox proportional hazards model, Cox extension, Fine Gray model, longitudinal studies, time-varying covariates

1. Introduction

In longitudinal studies, participants often experience death, a health outcome that might not be the event of interest (Lau, Cole, & Gange, 2009). In such a case, death, also referred to as censoring, removes study subjects who have not developed the event of interest from the at-risk segment of the study population (Sapir-Pichhadze et al., 2016). Death, then, becomes a competing risk, which is defined as any health event having the potential to alter the observation or expression of an event of interest (Andersen, Geskus, Witte, & Putter, 2012; Kohl, Plischke, Leffondre, & Heinze, 2015). When death is ignored, the occurrence of a study outcome different from death is expressed as the cumulative incidence, which can be estimated as the reverse of survival probabilities of the Kaplan-Meier product limit estimator (Noordzij et al., 2013; Austin, Lee, & Fine, 2016). Such an estimation, which relies on the assumption of the independence of censoring, can be responsible of an upward bias in the expression of the cumulative incidence (Berry, Ngo, Samelson, & Kiel, 2010; Koller, Raatz, Steyerberg, & Wolbers, 2012; Haller, Schmidt, & Ulm, 2013). The cumulative incidence function, to the contrary, allows accounting for the presence of death as a competing risk and provides a more accurate estimation of the incidence of a health event (Austin et al., 2016). The cumulative incidence function expresses the probability of occurrence of an event of interest conditional to surviving both that event and the competing risk (Pintilie, 2011; Dignam, Zhang, & Kocherginsky, 2012).

Fine and Gray (1999) introduced a technique for modeling the effect of covariates on an outcome in the presence of competing risk of death considering the proportional subdistribution hazards, providing a more accurate estimation of the effect of risk factors compared to the cause-specific hazards, which is the method applied in the Cox proportional hazards modeling approach. The cause-specific hazard provides an estimate of the probability of the hazards of the event of interest among the at-risk population without consideration for censored individuals (Baena-Díez et al., 2016). Modeling with the proportional subdistribution hazards maintains the pool of individual deceased from a cause different from the outcome of interest in the at-risk set of study participants (Haller et al., 2013; Boucquemont et al., 2014). However, this technique does not take into consideration the fact that during the course of a cohort study values of covariates may change with time, introducing the notion of time-varying

covariates (Berry et al., 2010).

In the presence of time-varying covariates, the proportionality hazards assumption, which is the basis of the Cox proportional hazards methodology, is no longer relevant (Agnihotram, Binder, & Frei, 2011; Anavatan & Karaoz, 2013; Thomas & Reyes, 2014). Estimates of the effect of covariates may be biased if modeling is performed ignoring the possibility of the variation of the values of these variables over time (Dekker et al., 2008) since the Cox proportional hazards method estimates an average hazards overtime (Therneau, Crowson, & Atkinson, 2018). Consequently, extensions of the Cox modeling approach, accounting for the changes in the values of covariates during the course of the study, can be used (Agnihotram et al., 2011; Anavatan & Karaoz, 2013; Thomas & Reyes, 2014).

In health outcomes research using longitudinal design, particularly cancer research among the elderly, investigators usually acknowledge the importance of competing risk of death and time-varying covariates, which they account for during statistical analyses (Noordzij et al., 2013; Berry et al., 2010). In cardiovascular cohort studies, however, researchers do not systematically account for these concepts when estimating the effect of covariates on a health outcome (Austin et al., 2016; Dekker et al., 2008). In this study, we aimed to model and compare the estimates of the effect of risk factors on the hazards of coronary heart disease (CHD) using the Cox proportional hazards model, Cox extension with time-varying covariates, and the Fine Gray methodology. We were seeking to provide an answer to the following question: "do coefficient estimates obtained when modeling the effect of risk factors on the hazards of CHD vary significantly when considering the influence of the competing risk of death and time-varying covariates?"

2. Method

2.1 Data Source and Study Population

We examined data from the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (NHEFS), a health cohort study conducted between 1971 and 1992 by the National Center for Health Statistics. The goal of the NHEFS was to assess the association between risk factors and morbidity, mortality, and hospitalization in the population of the United States [US] (Cox et al., 1997). The NHEFS included a baseline evaluation, which was a component of the First National Health and Nutrition Examination Survey conducted from 1971 to 1974 and three follow-up evaluations performed from 1982 to 1984, in 1987, and in 1992. The NHEFS targeted the segment of the US adult population aged between 25 and 74 years. For this analysis, we selected a sample of 6346 individuals with no previous history of CHD at baseline and who were followed until the last evaluation. A comprehensive description of the NHEFS along with data collection procedures are available elsewhere (Cox et al., 1997; Cox et al., 1992; Centers for Disease Control and Prevention [CDC], 2017a).

2.2 The Variables and Their Measurements

We defined a CHD event, the study outcome, as the first occurrence of a CHD episode either fatal or non-fatal. We calculated the time variable as the time to a CHD event or the time to death, whichever

was observed first.

The socio-demographic variables included age, race, sex, education, income, and body mass index (BMI). We described age both as a continuous variable expressed in years and as a categorical variable with two strata: "25-49" and "50-74" for participants aged 25 to 49 years and those aged 50 to 74 years respectively. We divided race into two groups: "White" for the participants who identified as White and "Non-White" for all other participants. We categorized sex as "male" and "female". We coded education into two groups expressed in a "yes/no" layout based on whether or not participants attained a graduate level education. We categorized income in two levels: "< $25,000" and "$25,000 and more" based on whether study participants had an annual income below $25,000 or an income equals to or above $25,000. We calculated BMI, using the measured weight (in lbs.) and height (in inches) according to the formula (weight/ height^2) × 703 **(**CDC, 2017b). We described BMI as a continuous variable and defined a two-level categorical variable as well based on whether study participants had a BMI < 30 and were referred to as "non-obese" or a BMI ≥ 30 and were referred to as "obese".

Other variables included comorbid conditions and behavioral characteristics. Among the comorbidities, we described diabetes and hypertension as dichotomous variables and coded them in a "yes/no" format according to answers provided by participants when asked if they had experienced the conditions. We considered cholesterol both as a continuous variable expressed in mg/dL and as a binary variable with two levels: "normal or low cholesterol" for blood cholesterol levels equal to or lower than 240mg/dL and "high cholesterol" for levels higher than 240mg/dL. The behavioral features included smoking, alcohol use, and physical activity. We coded all behavioral variables as binary variables expressed in "yes/no" layout based on whether or not the study participants have been engaging in these behaviors.

2.3 Statistical Analysis

We described study participants across their BMI status and used t-test or chi-square test for comparison across BMI levels whichever was appropriate.

We designed three multivariate models with CHD event as the outcome and all socio-demographic and behavioral variables as well as comorbid conditions as predictors. We referred to these models as the "Cox", the "time-varying covariates (TVC)", and the "Fine Gray" model using the Cox proportional hazard method, Cox extension with time-varying covariates, and the Fine Gray methodology respectively. Time-varying covariates included age, BMI, hypertension, stroke, diabetes, cholesterol, smoking, alcohol, and physical activity considering different values of these variables during the three study's follow-up evaluations.

We compared coefficient estimates for BMI, age, cholesterol, smoking, and diabetes taken up to four decimal places as used by Liao et al. (2009) according to the formula: $x^2 = \Sigma\ w_i\ (b_i - B)^2$. In this equation, b_i represents the variable coefficients of the ith models; w_i, the inverse variances of the coefficients ($1/SE_i^2$); and B*,* the weighted average of the coefficients of the 3 models, calculated as $B = (\Sigma\ w_i\ b_i)/(\Sigma\ w_i)$. This function has a chi-square distribution with two degrees of freedom (Liao et al., 2009). We performed all analyses using SAS 9.4 (Cary, NC) and considered a level of significance α =

0.05.

3. Result

3.1 Characteristics of the Study Population

In this study, participants, on average, were 48 years-old; however, a slight majority (52.74%) was under the age of 50 (Table 1). Most of the participants (86.75%) were white and 54.63% of them were females. On average, the study cohort had a serum cholesterol level of 221.99 mg/dL. Furthermore, for 31.39% of them the serum cholesterol level was higher than 240 mg/dL and for 15.96% of them the BMI was equal to or greater than 30. Regarding socioeconomic status, 6.18% of study participants had a graduate level education and 6.20% had an annual income equals to or greater than $25,000. Comorbidities seen during the study period included diabetes, hypertension, and stroke affecting 4.18%, 11.05%, and 1.36% of the study population respectively. The majority of participants (74.77%) consumed alcohol, 37.09% smoked cigarettes, and 90.04% reported they were involved in some form of physical activity. After an average follow-up of 16.24 years, 382 participants experienced a first CHD event corresponding to a cumulative incidence of 9.93% (Figure 1) and 1364 died from causes different from a CHD event.

Table 1. Characteristics of Participants of the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study at Enrollment, United States, 1971-1992

Characteristics	**Total**	**BMI < 30**	**BMI ≥ 30**	***P*** [a]
Participants, n (%)	6346 (100)	5333 (84.04)	1013 (15.96)	
CHD events (%)	382 (100)	280 (73.30)	102 (26.70)	< 0.001
Number of deaths, %	1364 (21.49)			
Follow-up time, mean, years	16.24			
Age, mean (SD), years	48.11 (14.05)	47.59 (14.10)	50.87 (13.46)	< 0.001
Age group (%)				< 0.001
25 to 49	3347 (52.74)	2913 (87.03)	434 (12.97)	
50 to 74	2999 (47.26)	2420 (80.70)	579 (19.30)	
Sex (%)				< 0.001
Male	2879 (45.37)	2503 (86.93)	376 (13.06)	
Female	3467 (54.63)	2830 (81.63)	637 (18.37)	
Race (%)				< 0.001
White	5505 (86.75)	4701 (85.39)	804 (14.60)	
Non-White	841 (13.25)	632 (75.15)	209 (24.85)	
Education (%)				< 0.001
College or less	6315 (93.82)	5309 (84.07)	1006 (15.93)	

Graduate level	390 (6.18)	360 (92.30)	30 (7.69)	
Family income[b] (%)				< 0.001
< $25,000	5714 (93.80)	4772 (83.51)	942 (16.49)	
≥ $25,000	378 (6.20)	349 (92.32)	29 (7.67)	
Diabetes (%)				< 0.001
Yes	265 (4.18)	193 (72.82)	72 (27.17)	
No	6081 (95.82)	5140 (84.52)	941 (15.47)	
Hypertension (%)				< 0.001
Yes	701 (11.05)	499 (71.19)	202 (28.82)	
No	5645 (88.95)	4834 (85.63)	811 (14.37)	
Stroke (%)				0.20
Yes	86 (1.36)	68 (79.07)	18 (20.93)	
No	6260 (98.64)	5265 (84.11)	995 (15.89)	
Smoking (%)				< 0.001
Yes	2354 (37.09)	2071 (87.98)	283 (12.02)	
No	3992 (62.91)	3212 (81.71)	730 (18.29)	
Alcohol (%)				< 0.001
Yes	4745 (74.77)	4060 (85.56)	685 (14.44)	
No	1601 (25.23)	1273 (79.51)	328 (20.49)	
Physical activity (%)				< 0.001
Yes	5714 (90.04)	4836 (84.63)	878 (15.37)	
No	632 (9.96)	479 (78.64)	135 (21.36)	
Cholesterol, mean (SD), mg/dL	221.99 (46.5)	219.93 (46.04)	232.83 (47.73)	<0.001
High cholesterol[c] (%)				< 0.001
Yes	1992 (31.39)	1578 (79.22)	414 (20.78)	
No	4354 (68.61)	3755 (86.24)	599 (13.76)	

Abbreviations: BMI = body mass index; SD = standard deviation; n = sample size

[a]*P*: P-values obtained from t-test, for continuous variables and chi-square test, for categorical variables.

[b]Annual family income; taking inflation into account, $25,000 in December of 1975 would approximately worth $113,912 in October of 2018 (United States [US] Department of Labor Bureau of Labor Statistics, 2018).

[c]High cholesterol: serum cholesterol level that is higher than 240mg/dL.

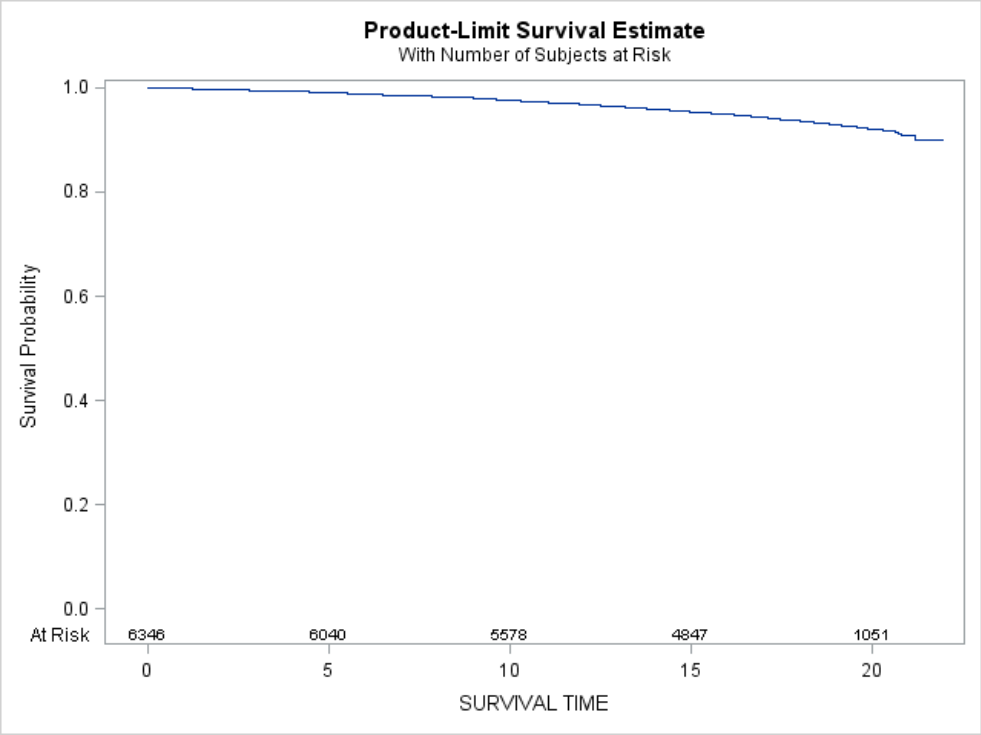

Figure 1. Graph of Survival Probabilities of Occurrence of a Coronary Heart Disease Event among Participants of the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (n = 6346), United States, 1971-1992. We Used the Kaplan Meier Methodology to Determine the Survival Probabilities and Deducted the Cumulative Incidence as the Reverse of the Survival Probabilities. The Survival Rate for the Study Population Was 90.07%, Corresponding to a Cumulative Incidence of 9.93%.

3.2 Effect of Covariates on the Hazards of CHD

The modeling of the estimates of the effects of covariates on the hazards of CHD using the Cox proportional hazard model, Cox extension with time-varying covariates, and the Fine Gray methodology fitting the "Cox", the "TVC", and the "Fine Gray" models revealed three groups of predictors. First, we identified factors that were significant in the three methods. This group included BMI, age, sex, cholesterol, diabetes, alcohol, and smoking (Table 2). We also observed factors such as race, income, education, and stroke that were not significant in any of the models. Finally, we saw that hypertension and physical activity were significant in the "Cox" and "TVC" models but were not significant in the "Fine Gray" model.

Table 2. Estimates of the Hazards of Coronary Heart Disease Obtained from Modeling Using Cox Proportional Hazards Method, Cox Extension with Time-Varying Covariates, and Fine-Gray Method in the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, United States, 1971-1992

Variables	Cox model[a]		TVC model[b]		Fine Gray model[c]	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**(95% CI)**
BMI	1.05	(1.03, 1.07)	1.05	(1.03, 1.07)	1.05	(1.03, 1.07)
Age group, years						
50 to 74	4.65	(3.57, 6.04)	4.65	(3.57, 6.04)	3.60	(2.76, 4.71)
Race						
White	1.20	(0.88, 1.63)	1.20	(0.88, 1.63)	1.34	(0.99, 1.83)
Sex						
Female	0.44	(0.35, 0.54)	0.44	(0.35, 0.54)	0.49	(0.39, 0.60)
Family income[d]						
≥ $25,000	0.72	(0.42, 1.25)	0.72	(0.42, 1.25)	0.76)	(0.44, 1.32)
Education level						
Graduate	0.94	(0.72, 1.24)	0.94	(0.72, 1.24)	0.99	(0.75, 1.30)
High cholesterol						
Yes	1.60	(1.31, 1.97)	1.60	(1.31, 1.97)	1.59	(1.29, 1.97)
Diabetes						
Yes	2.40	(1.71, 3.36)	2.40	(1.71, 3.36)	2.01	(1.41, 2.85)
Hypertension						
Yes	1.39	(1.04, 1.85)	1.39	(1.04, 1.85)	1.32	(0.98, 1.76)
Stroke						
Yes	1.82	(0.96, 3.43)	1.82	(0.96, 3.43)	1.16	(0.61, 2.20)
Alcohol						
Yes	0.64	(0.51, 0.81)	0.64	(0.51, 0.81)	0.67	(0.53, 0.84)
Physical activity						
Yes	0.71	(0.53, 0.96)	0.71	(0.53, 0.96)	0.85	(0.62, 1.14)
Smoking						
Yes	1.68	(1.35, 2.09)	1.68	(1.35, 2.09)	1.52	(1.22, 1.90)

Abbreviations: HR = hazards ratio; TVC = time-varying covariates; BMI = body mass index; CI = confidence interval

[a]Multivariate model obtained using the Cox proportional hazards method.

[b]Multivariate model obtained using Cox extension with time-varying covariates (e.g., BMI, hypertension,

stroke, diabetes, cholesterol, smoking, alcohol, and physical activity).

[c]Multivariate model obtained using the Fine Gray method considering the influence of the competing risk of death.

[d]Annual family income: considering inflation, $25,000 in December of 1975 would approximately worth $113,912 in October of 2018 (US Department of Labor Bureau of Labor Statistics, 2018

3.3 Comparison of the Coefficients Estimates

The hazards ratio estimates and their corresponding confidence intervals (CIs) for all factors remained unchanged in the "Cox" and the "TVC" models whereas all estimates except those for BMI varied in the "Fine Gray" model compared to the other two models (Table 2). We, however, found no significant difference comparing estimates from the three models. For all predictors, we obtained a *P*-value > 0.05 when applying the test by Liao et al. (1999) (Table 3).

Table 3. Comparison of Coefficient Estimates Obtained When Modeling the Effect of Covariates on the Hazards of Coronary Heart Disease with their Corresponding *P*-Values in the First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study, United States, 1971-1992

Covariates	Model[a]	β	SE	*P*[b]
BMI	Cox	0.0499	0.0094	> 0.05
	TVC	0.0500	0.0094	
	Fine Gray	0.0512	0.0096	
Age	Cox	1.5363	0.1339	> 0.05
	TVC	1.5364	0.1339	
	Fine Gray	1.2813	0.1365	
Cholesterol	Cox	0.4730	0.1048	> 0.05
	TVC	0.4730	0.1048	
	Fine Gray	0.4650	0.1082	
Smoking	Cox	0.5192	0.1109	> 0.05
	TVC	0.5192	0.1109	
	Fine Gray	0.4197	0.1127	
Diabetes	Cox	0.8746	0.1725	> 0.05
	TVC	0.8746	0.1725	
	Fine Gray	0.6960	0.1797	

Abbreviations: β = coefficient estimates; SE = standard error; BMI = body mass index

[a]Estimates were obtained from three models: 1) "Cox" standing for the Cox proportional hazard model; 2) "TVC" standing for time-varying covariates model; and 3) "Fine Gray" standing for the Fine Gray model.

[b]*P*: P-values obtained by comparing the coefficient estimates using the test by Liao at al. (1999). In this analysis, the test has a chi-square distribution with two degrees of freedom.

4. Discussion

In this study, we aimed to investigate the influence of competing risk of death and time-varying covariates on estimates of the effect of risk factors on the hazards of CHD. We found no significant difference between coefficient estimates when modeling using the Cox proportional hazards method, Cox extension with time-varying covariates, and the Fine Gray method. Our findings differed from results of many cohort studies exploring cardiovascular and non-cardiovascular outcomes. In their investigation of the effect of diabetes on the risk of cardiovascular mortality among individuals aged 35 to 79 years over a ten-year follow-up period, Baena-Díez et al. (2016) found a decrease in coefficient estimates while modeling taking the competing risk of death into consideration compared to the Cox proportional hazards methodology. Baena-Díez et al. (2016) formulated their conclusion simply considering the difference in magnitude of the estimates of the effect of the risk factors without testing the statistical significance of the observed difference. In our analysis, we did notice a decrease in coefficient estimates for all covariates except BMI when we accounted for the competing risk of death. However, the difference was not statistically significant.

Similarly, a decrease in coefficient estimates was observed by Berry et al. (2010) who reported a reduction in the relative hazards of second hip fracture among a geriatric population when using the competing risk of death regression approach by Fine Gray compared to the Cox proportional hazards method. Berry et al. (2010) also demonstrated a correlation between the decrease in coefficient estimates and the length of the observation period whereby lower effect estimates were obtained with longer observation periods. In addition, in their study, the average age of the participants influenced the magnitude of the difference between the two methodologies. The influence of age might be due to the fact that the risk of death is higher among older individuals as opposed to younger segments of the population. Both factors can be considered as playing a modifying role in the findings by Berry et al. (2010) who observed their cohort over a period of ten years. Berry et al. (2010) did not use any statistical approach to test the significance of the difference in the obtained estimates.

With regards to modeling considering time-varying covariates, Warwick et al. (2004) did not find any significant change in coefficients estimates in their modeling of varying values of the effect of tumor size, lymph node status, and tumor grade on the hazards of death due to breast cancer while comparing estimates obtained from the Cox proportional hazards method during the twenty-year follow-up period of the Swedish Two-County Trial. Even though the outcome and predictors used by Warwick et al. (2004) were different from ours, their findings supported our observation of no effect considering the

variation of covariates over time when opposed to fixed covariates during the modeling of the effect of risk factors on a health outcome. Warwick et al. (2004) justified their findings through the assumption of a consistency of the relative hazards of the outcome over time. From their perspective, the relative difference in the hazards would not change for two levels of a factor throughout the duration of a study. In another cohort study, Murphy et al. (2011) observed a 12.5% reduction in the relative risk of disabilities among elderly individuals aged 70 years and older for the variable age in a time-varying covariate model as opposed to a fixed-covariates procedure. In our study, which also included age as a covariate, the coefficient estimates remained unchanged in the time-varying covariate model when compared to the Cox proportional hazards approach for that variable. The difference in estimates observed by Murphy et al. (2011) might be due to several factors. First, they performed a Poisson regression model considering fixed and time-varying covariates while we used the Cox method and an extension with time-varying covariates. In addition, the mean age of their cohort was 78.4 years-old and over the course of their 108-month observation period, 43.8% of their study participants died whereas in our study, after an average 16 years of follow-up, 21.49% of our cohort were dead. Murphy et al. (2011) attributed the reduction in relative risk in their outcome over time to the effect of death. However, they did not test the statistical significance of the difference in estimates.

5. Limitations

Few authors have explored the concepts of competing risk of death and time-varying covariates in cohort studies with cardiovascular outcomes. We could not compare our findings to those of studies using methodologies and variables matching ours. Nonetheless, we put our results side by side to those of Baena-Díez et al. (2016), Berry et al. (2010), Warwick et al. (2004), and Murphy et al. (2011). These authors were not all investigating cardiovascular outcomes. While Baena-Díez et al. (2016) were examining the influence of competing risk of death on risk factor estimates for cardiovascular death. Berry et al. (2010) used second hip fracture as their outcome to demonstrate the effect of competing risk of death on risk factor estimates in a cohort of elderly individuals. Warwick et al. (2004) investigated the influence of time-varying covariates on breast cancer death in an all-female cohort with invasive breast carcinoma. Murphy et al. (2011) demonstrated the effect of time-varying covariates by fitting repeated models over time to estimate the number of disabilities of daily living. In addition, none of these researchers estimated the significance of their findings through statistical testing. Despite these constraints, those studies were valuable assets that allowed us to compare and discuss our findings.

6. Conclusion

Estimates obtained when modeling the effect of risk factors on the hazards of CHD did not vary significantly when accounting for the influence of competing risk of death and time-varying covariates. More cohort studies focusing on cardiovascular outcomes are necessary to investigate the influence of

those concepts on coefficient estimates of predictor variables. We support the recommendations by Austin et al. (2016) suggesting to authors of longitudinal studies to always report their findings considering all causes, cause-specific hazards functions, and sub-distribution hazards functions when modeling the association of risk factors and outcomes.

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