Time-adjusted effect of socioeconomic status in mortality rates after brain injury: cohort study

DOCUMENT: SAR-2023-016-BH-v01

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TABLE OF CONTENTS

Time-adjusted effect of socioeconomic status in mortality rates after brain injury: cohort study

Document version

Version	Alterations
01	Initial version

1 ABBREVIATIONS

- FIM: Functional Independence Measure
- HR: hazards ratio
- SD: standard deviation
- SES: socioeconomic status

2 CONTEXT

This analysis expands on a previous analysis with a similar objective (**SAR-2023-004-BH-v02**), by employing more flexible modeling strategies to include time-dependent covariates that were dropped from the previous analysis. In the process the raw FIM scores were substituted by their quartiles.

2.1 Objectives

To determine the effect of socioeconomic status of the neighborhood on mortality of patients with brain injury, accounting for time-dependent covariates.

3 METHODS

The data procedures, design and analysis methods used in this report are fully described in the annex document **SAP-2023-016-BH-v01**.

This analysis was performed using statistical software R version 4.3.0.

4 RESULTS

4.1 Study population and follow up

There initially were 76,665 observations on 19,303 study participants considered for inclusion. After excluding follow up measurements during the COVID-19 pandemic to mitigate confounding on mortality causes there were 51,308 observations left in the study sample. After applying the inclusion criteria for the study period between 2010-01-01 and 2018-12-31 and considering the status at the last available follow up time for each individual a total of 7,409 participants were included in the analysis.

The epidemiological profile of the participant included in the study was a male participant (5,419 (73%)) with an average (SD) age of 45 (20) years. The average (SD) time of follow up was 3.06 (1.94) years.

Races were not homogeneously available in the study population with 4,936 (67%) individuals being white; 3,170 (43%) were single (never married) at the time of injury, and most participants were well educated with 3,363 (46%) at greater than high school level. A total of 4,377 (59%) were employed and 3,461 (48%) participants lived in an urban area.

Table 1 *Epidemiological, demographic and clinical characteristics of study participants.*

Characteristic	N = 7,409
SES quintiles, n (%)	
Prosperous	1,350 (22%)
Comfortable	1,239 (20%)
Mid-Tier	1,124 (19%)
At-Risk	1,167 (19%)
Distressed	1,194 (20%)
Unknown	1,335
Mortality, n (%)	998 (13%)
Time of follow up (years), Mean (SD)	3.06 (1.94)
Sex:, n (%)	
Male	5,419 (73%)
Female	1,984 (27%)
Unknown	6
What is your race?, n (%)	
White	4,936 (67%)
Black	1,143 (15%)
Hispanic	952 (13%)
Other	368 (5.0%)
Unknown	10
What is your marital status?, n (%)	
Single (Never Married)	3,170 (43%)

Married	2,589 (35%)
Divorced	921 (12%)
Separated	244 (3.3%)
Widowed	454 (6.1%)
Other	15 (0.2%)
Unknown	16
Age at Injury, Mean (SD)	45 (20)
Unknown	19
Substance Problem Use, n (%)	2,691 (38%)
Unknown	264
Education, n (%)	
Greater Than High School	3,363 (46%)
Less Than High School	1,379 (19%)
High School/GED	2,615 (36%)
Unknown	52
At time of injury, what was your employment status?, n (%)	
Employed	4,377 (59%)
Unemployed	794 (11%)
Other	2,204 (30%)
Unknown	34
Urbanization based on zip code of address at discharge., n (%)	
Suburban	2,190 (30%)
Rural	1,635 (22%)
Urban	3,461 (48%)
Unknown	123
Prior to this injury, has a physician ever told you that you have a seizure disorder?, n (%)	52 (5.6%)
Unknown	6,483
Spinal cord injury:, n (%)	432 (5.8%)
Unknown	19
Cause of injury:, n (%)	
Vehicular	3,324 (45%)
Violence	650 (8.8%)
Falls	2,541 (34%)
Other	873 (12%)
Unknown	21
Primary rehabilitation payor:, n (%)	
Private Insurance	3,868 (52%)
Public Insurance	2,914 (39%)
Other	600 (8.1%)
Unknown	27
Residence after rehab discharge:, n (%)	
Private Residence	5,857 (79%)
Other	1,531 (21%)
Unknown	21
Days From Injury to Rehab Discharge, Mean (SD)	46 (37)

FIM Motor at Discharge quartiles, n (%)	
Q1	1,850 (25%)
Q2	2,001 (27%)
Q3	1,704 (23%)
Q4	1,747 (24%)
Unknown	107
FIM Cognitive at Discharge quartiles, n (%)	
Q1	1,938 (26%)
Q2	1,884 (26%)
Q3	1,827 (25%)
Q4	1,726 (23%)
Unknown	34

The observed overall mortality was 13.5% in the study period. The distribution of cases appear homogeneous across SES quintiles (Figure 1), ranging from 10.6% to 13.5%. We will test the effect of SES quintiles on the hazard rate in the next section. See also Figure A2 in the appendix for the distribution of sexes in each SES quintile in the study population.

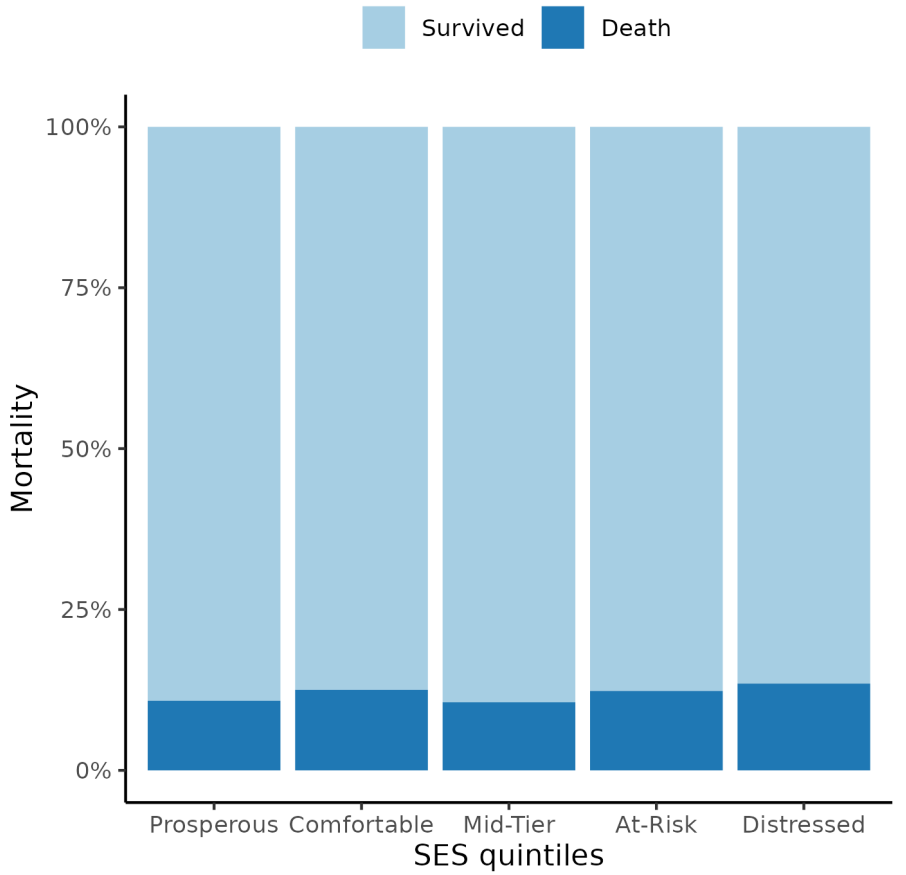

Figure 1 *Proportion of cases per SES quintiles.*

4.2 Time-dependent effect of SES on mortality

The previous seizure disorder diagnosis was missing for most of the study population and was not included in the model as a covariate to preserve study power. After excluding participants with missing data from other variables a total of 5,752 complete cases were available for analysis. The cause of injury and both FIM scales were removed from the model due to violations to the proportional hazards assumption (see Figure A4 in the appendix for the Schoenfeld residuals and p-values for each variable in the full model).

The survival curves of both sexes by SES quintiles can be seen in Figure 2. Overall, the distressed neighborhoods appear to have a lower survival probability then other neighborhoods. This appears to be true for both sexes, and males had a higher risk of dying than females in all neighborhoods. This plot was cropped at 50% survival for presentation purposes, see Figure A3 in the appendix for an uncropped version.

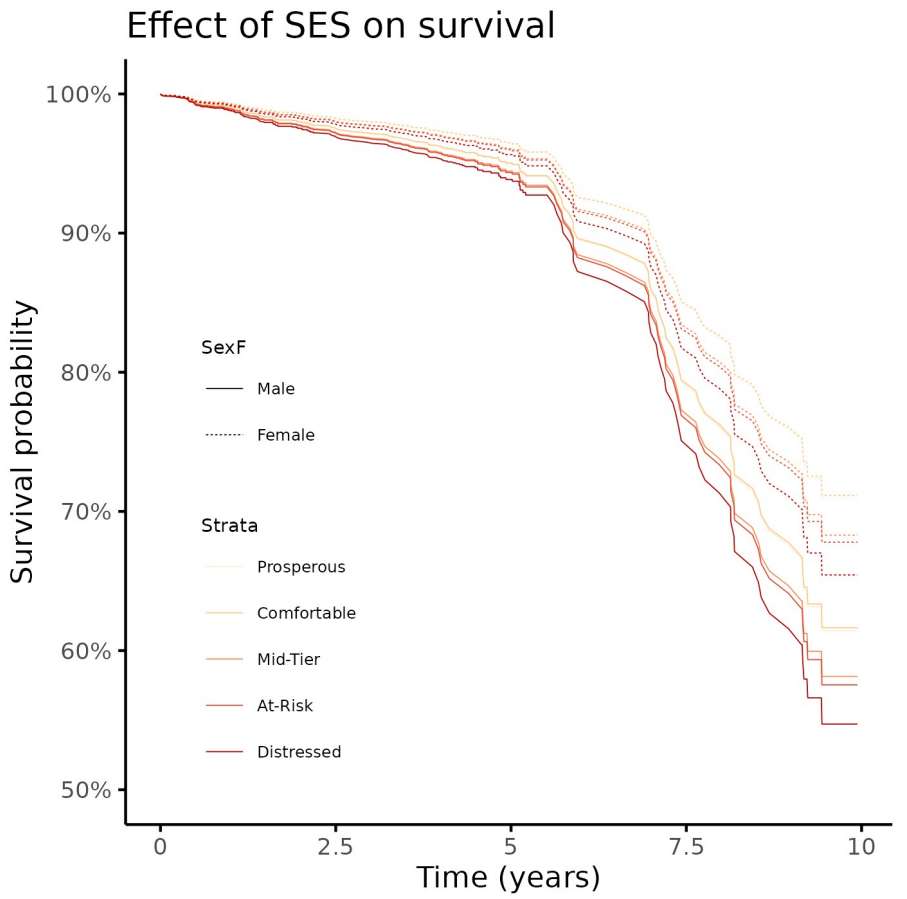

Figure 2 *Survival of participants, by sex and by SES quintiles.*

When considering only the crude effect of SES on mortality neighborhood to which the individuals were discharged was associated with mortality (Table 2). Participants who were discharged to an at-risk neighborhood had increased chance of dying (HR = 1.29, 95% CI = 1.02 to 1.64), when compared to those discharged to a prosperous neighborhood. Participants discharged to a distressed neighborhood also had a higher mortality risk (HR = 1.36, 95% CI = 1.08 to 1.71), when compared to those discharged to a prosperous neighborhood.

Table 2 *Effect of SES on mortality; HR estimates were adjusted for sex, race, age, substance abuse, education, employment status, urbanization, spinal cord injury, rehabilitation payer, residence after rehab discharge, FIM scores quartiles and stratified by cause of injury.*

	Crude estimate			Model 2			Model 3			Model 4		
Characteristic	**HR**[1]	**95% CI**[1]	**p-value**	**HR**[1,2]	**95% CI**[1]	**p-value**	**HR**[1,3]	**95% CI**[1]	**p-value**	**HR**[1,4]	**95% CI**[1]	**p-value**
SES quintiles												
Prosperous	—	—		—	—		—	—		—	—	
Comfortable	1.19	0.94 to 1.50	0.142	1.08	0.85 to 1.36	0.529	1.05	0.83 to 1.32	0.692	0.99	0.78 to 1.26	0.954
Mid-Tier	1.00	0.78 to 1.28	0.982	1.18	0.92 to 1.52	0.186	1.14	0.89 to 1.46	0.314	1.11	0.86 to 1.44	0.414
At-Risk	1.29	1.02 to 1.64	**0.033**	1.31	1.03 to 1.67	**0.026**	1.20	0.94 to 1.53	0.137	1.13	0.88 to 1.46	0.323
Distressed	1.36	1.08 to 1.71	**0.008**	1.39	1.09 to 1.77	**0.008**	1.27	0.99 to 1.62	0.060	1.24	0.96 to 1.59	0.099

[1]HR = Hazard Ratio, CI = Confidence Interval

[2]Adjusted by demographic variables

[3]Adjusted by demographic + clinical variables

[4]Adjusted by demographic + clinical + geographical variables

After controlling for all relevant covariates, this effect starts to disappear. It can only be consistently detected after controlling for demographic variables in at-risk and distressed neighborhoods. Additionally controlling for clinical (model 3) and geographical covariates (model 4) all estimates converge towards the null hypothesis.

Notes:

- note drift of point estimates
- note reliability of precision / CIs lengths don't change much
- possible evidence of confounding of the effect, after controlling for clinical + geo

5 OBSERVATIONS AND LIMITATIONS

Recommended reporting guideline

The adoption of the EQUATOR network (http://www.equator-network.org/) reporting guidelines have seen increasing adoption by scientific journals. All observational studies are recommended to be reported following the STROBE guideline (von Elm et al, 2014).

6 CONCLUSIONS

The epidemiological profile of the study participant is an 31 years old white male, that has greater than high school level of education, is actively employed and lives in an urban setting.

There appears to be a crude effect of SES on mortality, where participants that were discharged to either a comfortable or a distressed neighborhood had increased risk of death when compared to those discharged to a prosperous neighborhood. After controlling for other variables there is no association between SES and mortality.

7 REFERENCES

- **SAP-2023-016-BH-v01** – Analytical Plan for Time-adjusted effect of socioeconomic status in mortality rates after brain injury: cohort study
- **SAR-2023-004-BH-v02** – Effect of socioeconomic status in mortality rates after brain injury: cohort study
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014 Dec;12(12):1495-9 (https://doi.org/10.1016/j.ijsu.2014.07.013).

8 APPENDIX

8.1 Exploratory data analysis

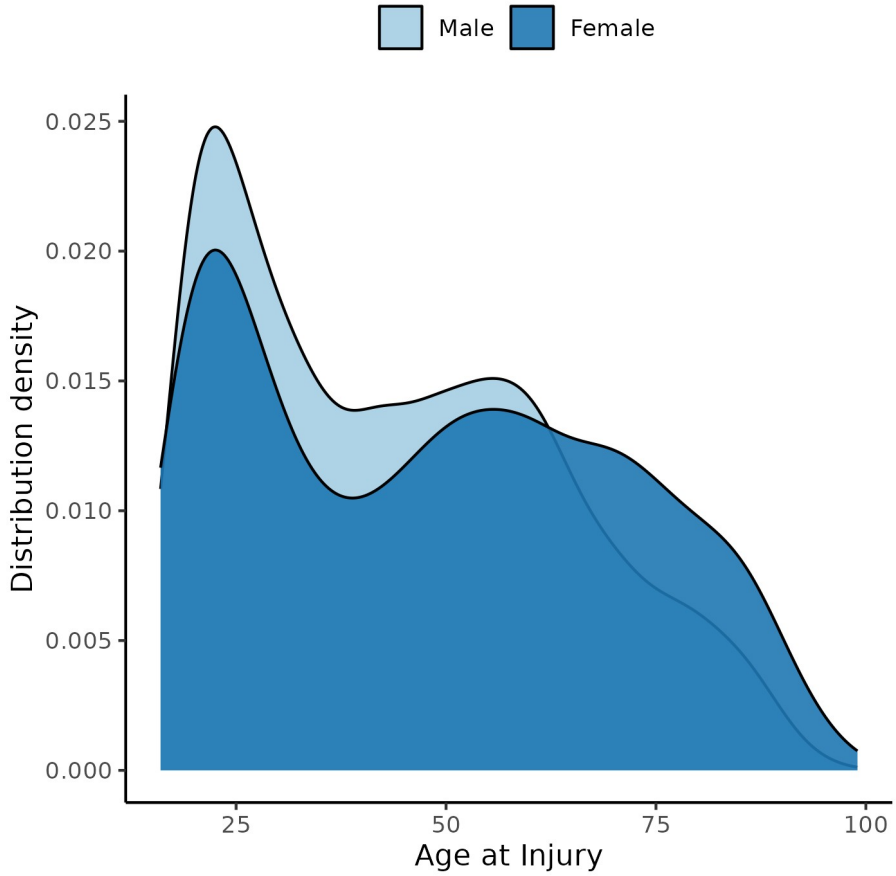

Figure A1 *Distribution of age in the study population.*

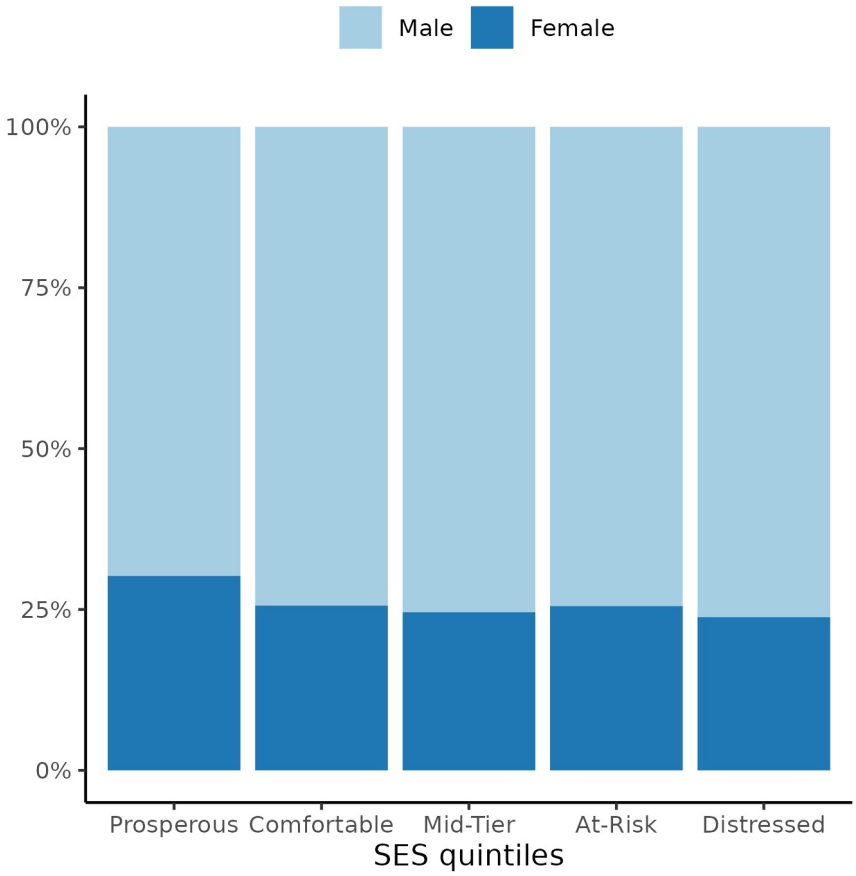

Figure A2 *Distribution of SES in the study population.*

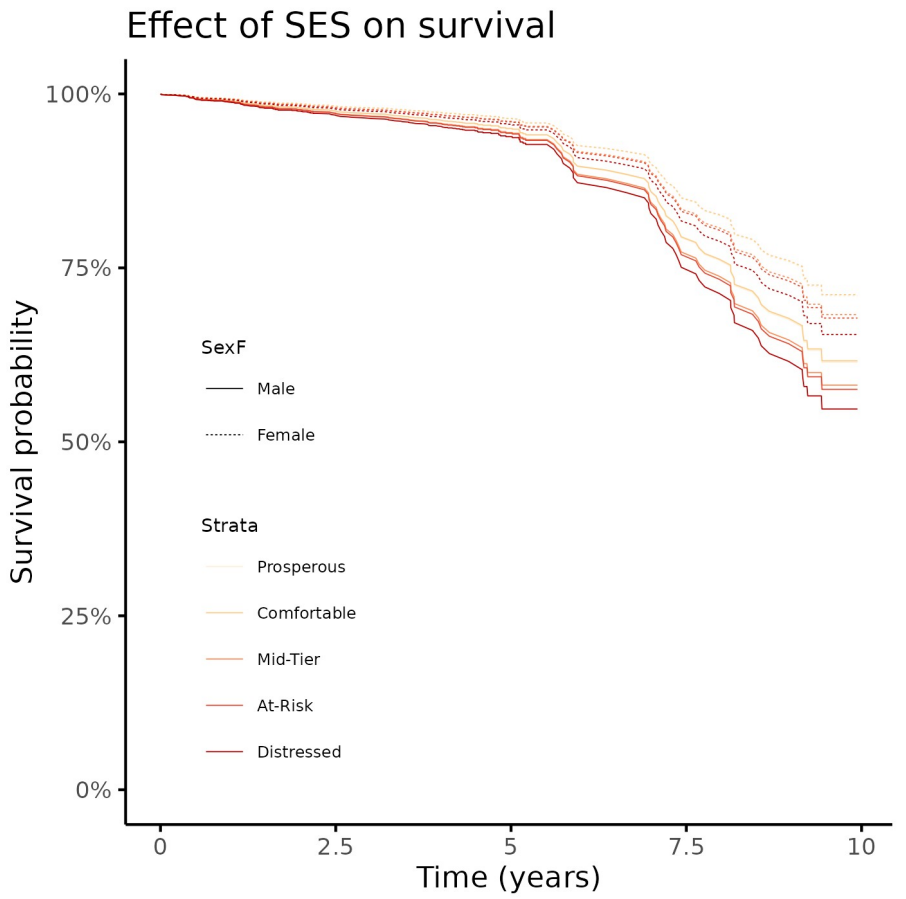

Figure A3 *Alternative version of figure 2.*

8.2 Modeling strategy

8.2.1 Approaches to control for time-dependent covariates

8.2.1.1 Schoenfeld and Martingale residuals

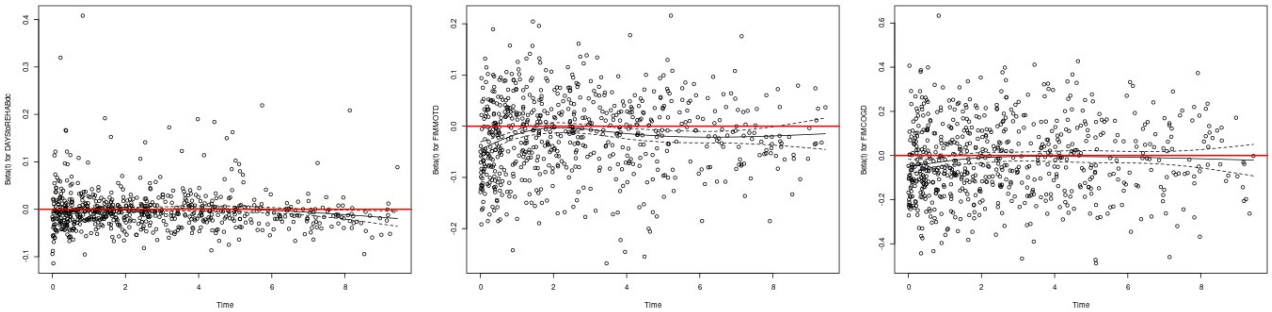

Figure A4 *caption*

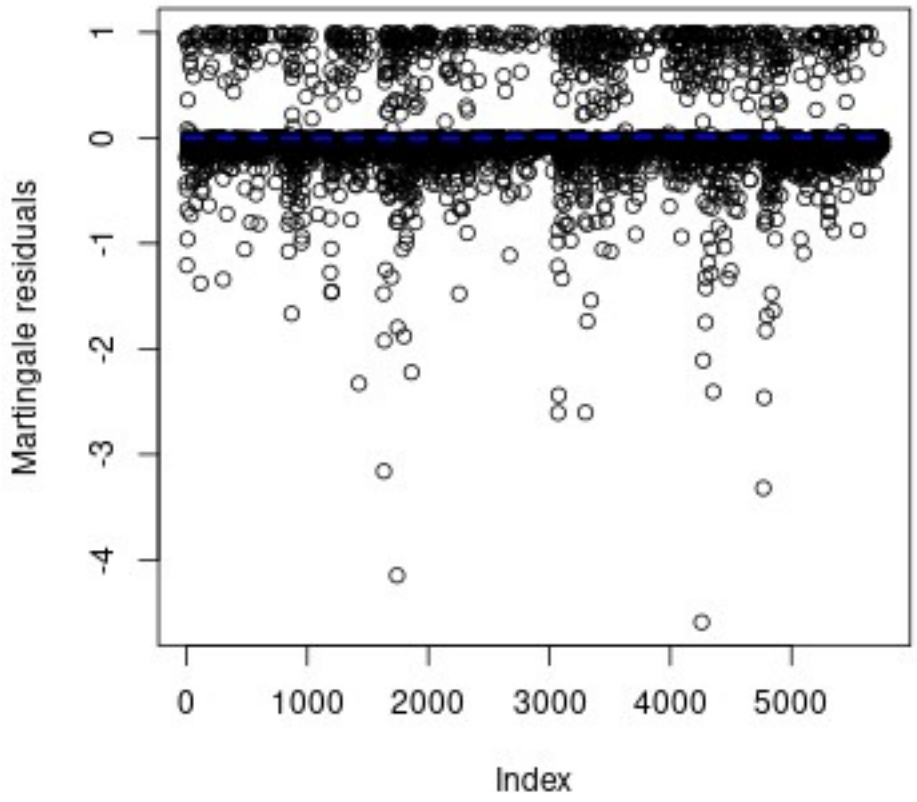

Figure A5 *caption*

Notes:

- cause, days, fimmot and fimcog are time-dependent (fail schoenfeld test) (A4)
- a few observations might be outliers, but do not appear to be influential (A5)

8.2.1.2 Martingale residuals of covariates against the null model

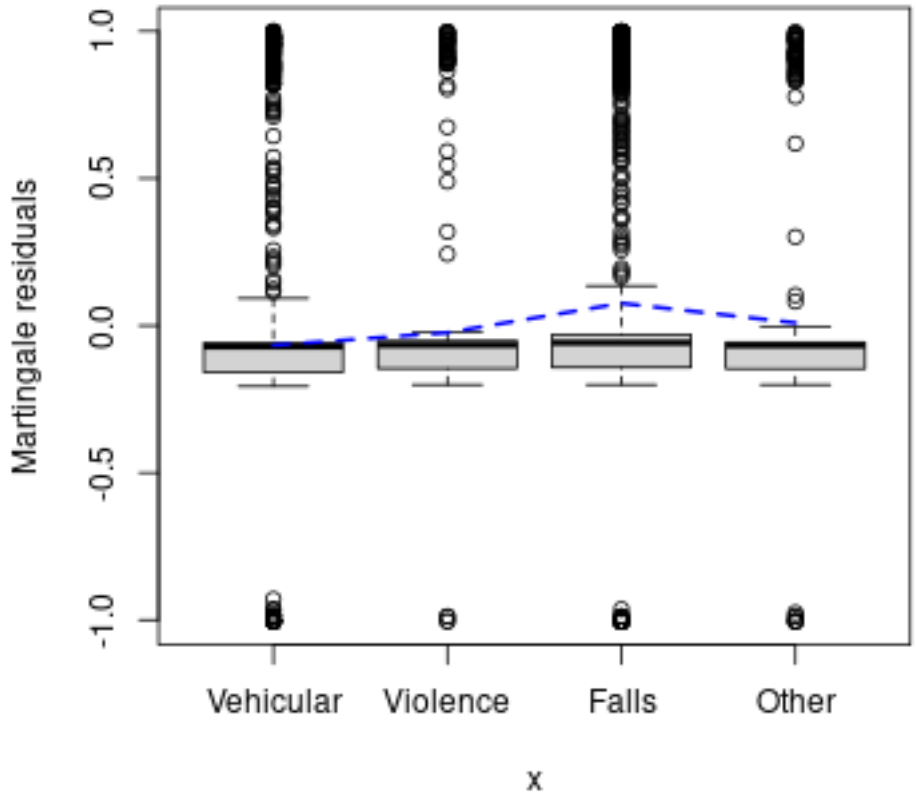

Figure A6 *caption*

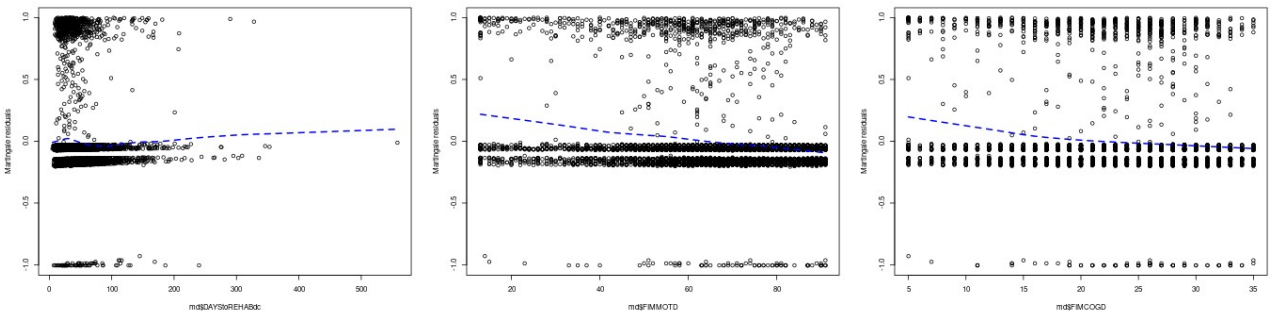

Figure A7 *caption*

Notes:

- Cause has an extreme non-PH violation, falls are much higher risk (A6)
- this justifies stratifying by Cause
- individuals with lower days/fimmot/fimcog have higher non-PH risk (A7)
- days is much worse than FIM scores (highly non-linear) (A7)

8.2.1.3 Stratification by cause of injury

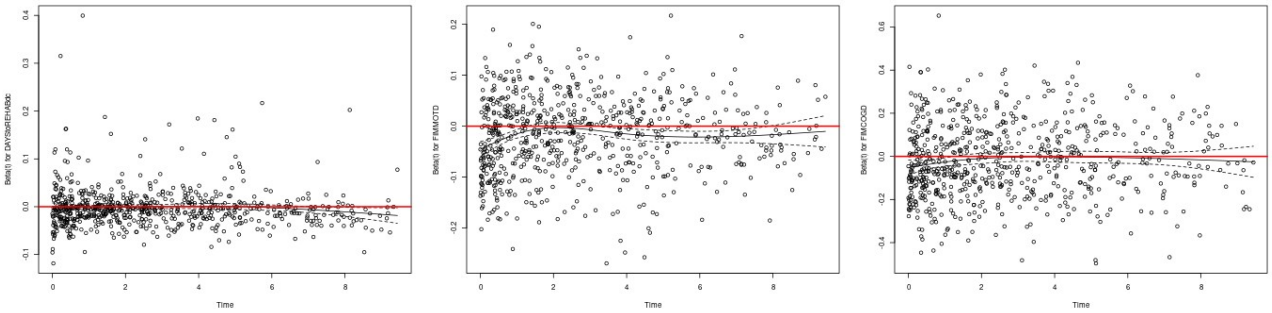

***Figure A8** caption*

Notes:

- stratifying by cause helps with non-PH of the 3 vars (A8)

8.2.1.4 Time split

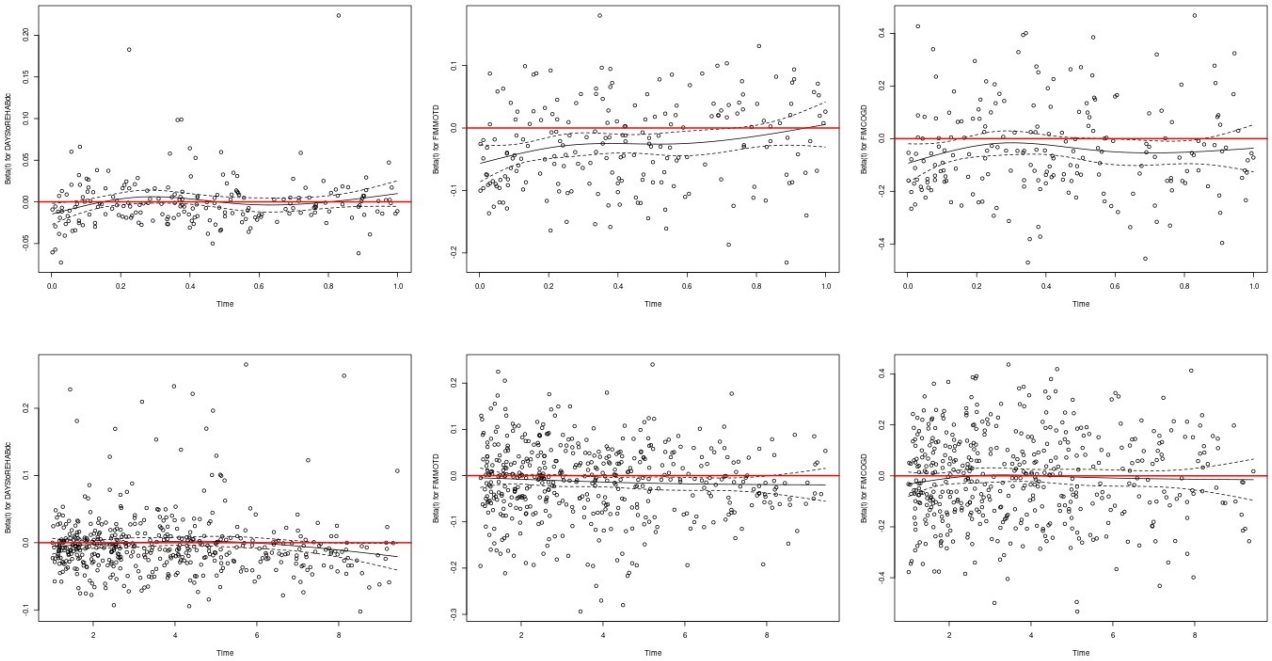

Figure A9 *caption*

Notes:

- time split at 1yr doesn't help further (A9)

8.2.1.5 Non-linear fitting

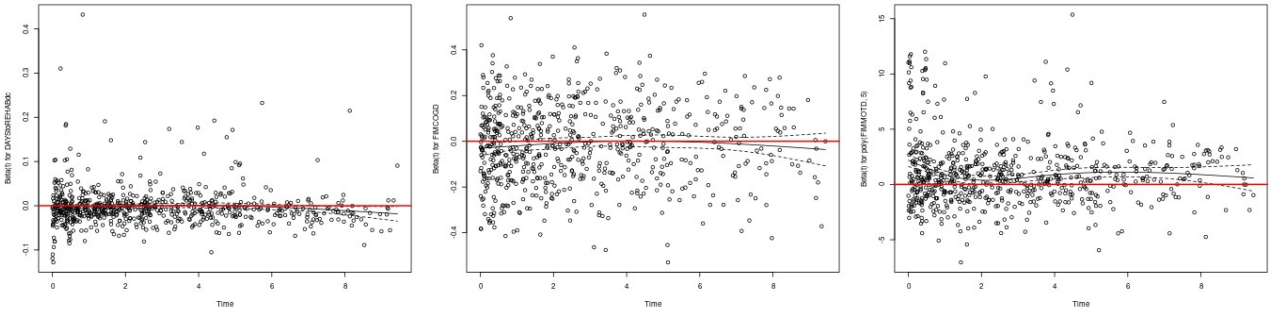

Figure A10 *caption*

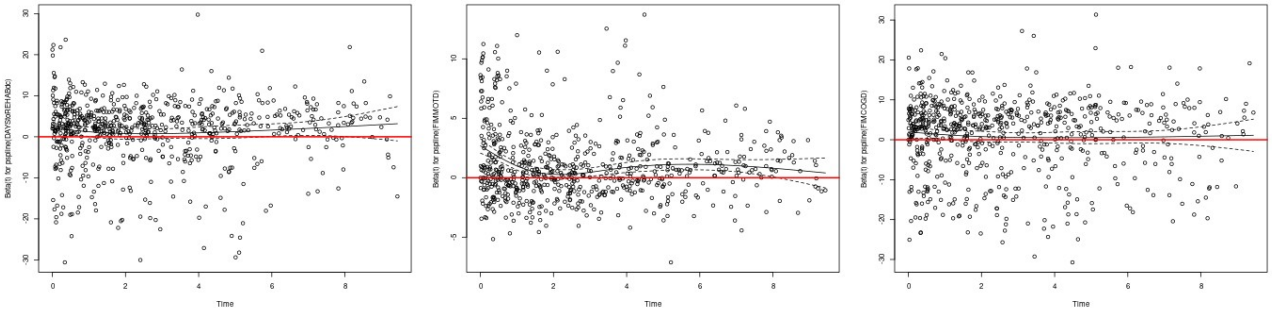

Figure A11 *caption*

Notes:

- polynomials (A10) and splines (A11) appear to help stabilize residuals, but not enough

8.2.1.6 Interaction with time

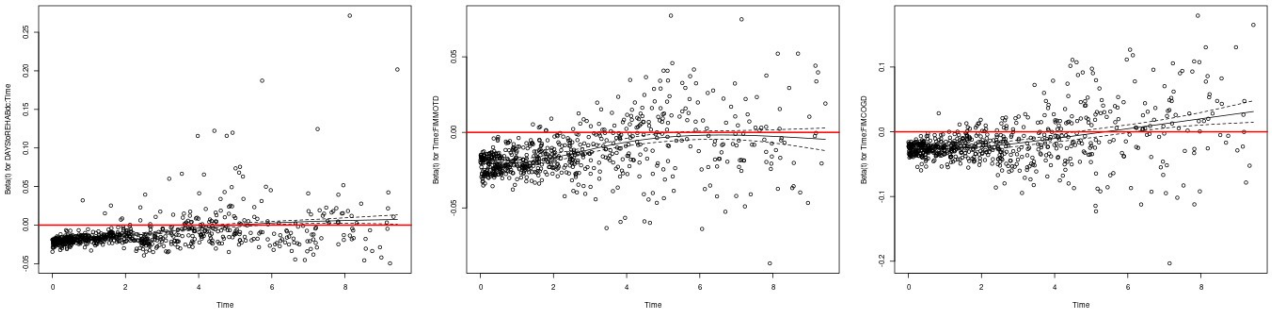

Figure A12 *caption*

Notes:

- makes non-PH worse, not helpful at all (A12)

8.2.1.7 FIM scores quartiles

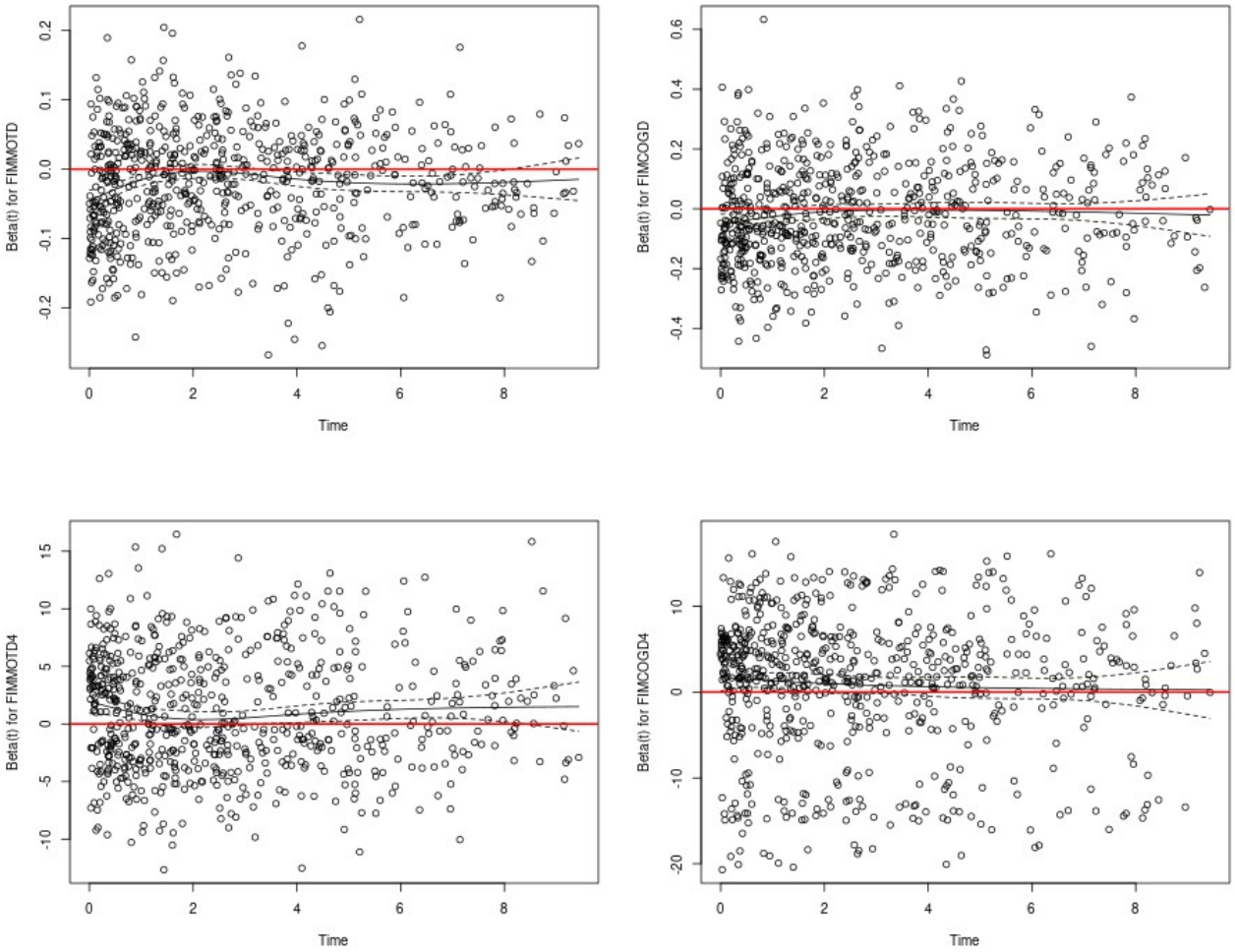

Figure A13 *caption*

Notes:

- days still non-PH (A13)
- FIM scores seem PH enough (A13)

8.2.2 Final model specification

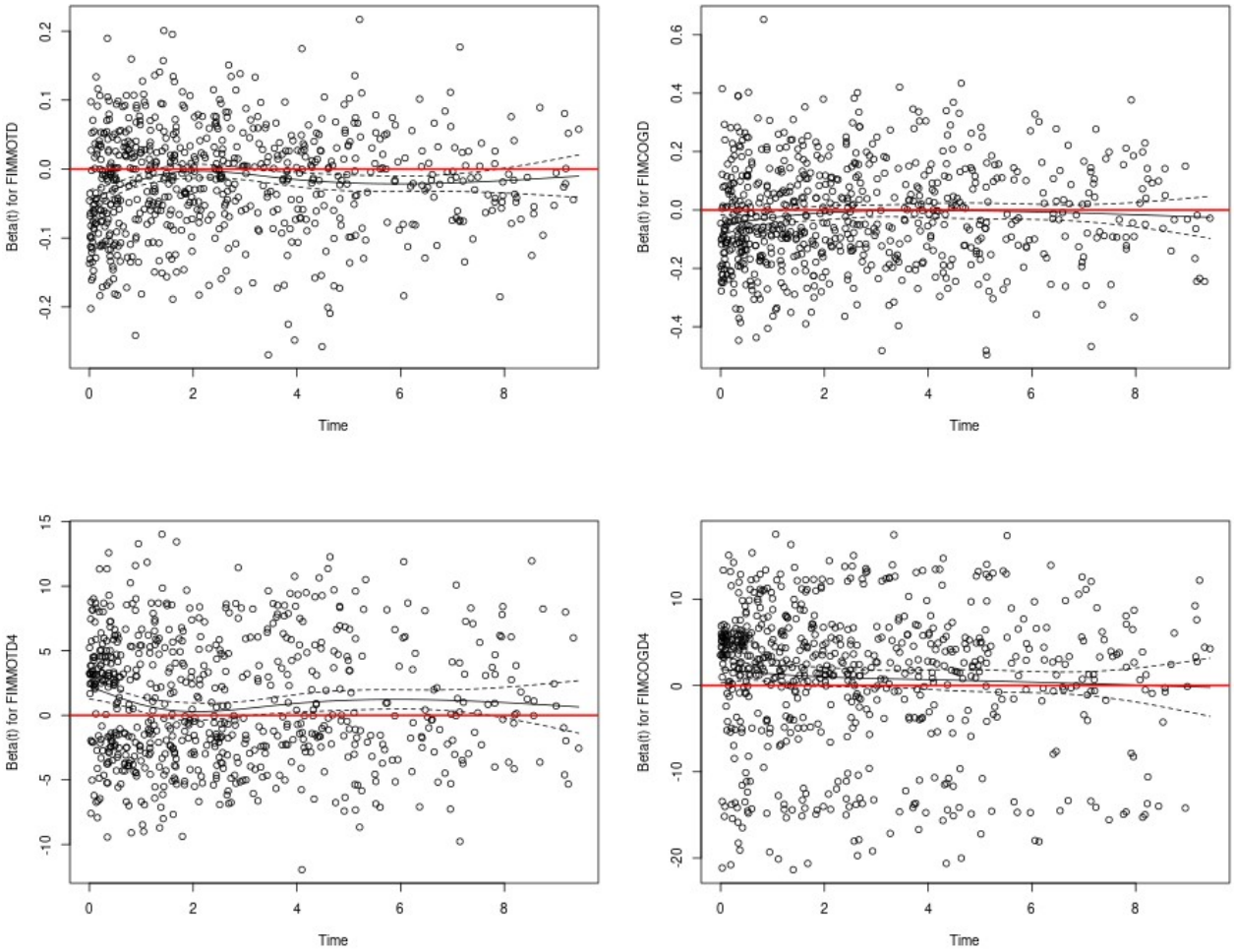

Figure A14 *caption*

Notes:

- removing days makes residuals appear PH (A14)
- passes schoenfeld test
- final model: strat by cause + FIM quartiles + drop days

***Table A1** Alternative version of Table 2, showing effects from all covariates included in the models.*

	Crude estimate	Model 2	Model 3	Model 4
Characteristic	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]
SES quintiles				
Prosperous	—	—	—	—
Comfortable	1.19 (0.118)	1.08 (0.119)	1.05 (0.119)	0.99 (0.122)
Mid-Tier	1.00 (0.126)	1.18 (0.127)	1.14 (0.128)	1.11 (0.131)
At-Risk	1.29* (0.120)	1.31* (0.122)	1.20 (0.124)	1.13 (0.128)
Distressed	1.36** (0.117)	1.39** (0.124)	1.27 (0.126)	1.24 (0.129)
Sex:				
Male		—	—	—
Female		0.64*** (0.089)	0.71*** (0.089)	0.70*** (0.090)
What is your race?				
White		—	—	—
Black		0.83 (0.117)	0.83 (0.120)	0.82 (0.122)
Hispanic		0.64** (0.162)	0.58** (0.165)	0.59** (0.169)
Other		0.73 (0.206)	0.70 (0.207)	0.71 (0.208)

	Crude estimate	Model 2	Model 3	Model 4
Characteristic	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]
Age at Injury		1.04*** (0.002)	1.04*** (0.003)	1.03*** (0.003)
Education				
Greater Than High School		—	—	—
Less Than High School		1.21 (0.114)	1.19 (0.116)	1.20 (0.116)
High School/GED		1.39*** (0.087)	1.37*** (0.088)	1.36*** (0.089)
At time of injury, what was your employment status?				
Employed		—	—	—
Unemployed		2.23*** (0.136)	1.70*** (0.143)	1.68*** (0.144)
Other		2.22*** (0.100)	1.75*** (0.106)	1.75*** (0.106)
Primary rehabilitation payor:				
Private Insurance			—	—
Public Insurance			1.31** (0.096)	1.32** (0.096)
Other			1.14 (0.185)	1.15 (0.186)
Spinal cord injury:			1.42* (0.176)	1.38 (0.176)

Characteristic	Crude estimate HR (SE)[1,2]	Model 2 HR (SE)[1,2]	Model 3 HR (SE)[1,2]	Model 4 HR (SE)[1,2]
Substance Problem Use			1.30** (0.094)	1.26* (0.095)
FIM Motor at Discharge quartiles				
Q1			—	—
Q2			0.62*** (0.099)	0.67*** (0.101)
Q3			0.58*** (0.117)	0.64*** (0.120)
Q4			0.49*** (0.137)	0.54*** (0.141)
FIM Cognitive at Discharge quartiles				
Q1			—	—
Q2			0.84 (0.104)	0.85 (0.104)
Q3			0.83 (0.111)	0.84 (0.111)
Q4			0.64*** (0.127)	0.67** (0.128)
Residence after rehab discharge:				
Private Residence				—
Other				1.40*** (0.089)

Characteristic	Crude estimate HR (SE)[1,2]	Model 2 HR (SE)[1,2]	Model 3 HR (SE)[1,2]	Model 4 HR (SE)[1,2]
Urbanization based on zip code of address at discharge.				
Suburban				—
Rural				1.05 (0.116)
Urban				1.07 (0.097)

[1]*p<0.05; **p<0.01; ***p<0.001

[2]HR = Hazard Ratio, SE = Standard Error

8.3 Availability

All documents from this consultation were included in the consultant's Portfolio.

The portfolio is available at:

https://philsf-biostat.github.io/SAR-2023-016-BH/

8.4 Associated analyses

This analysis is part of a larger project and is supported by other analyses, linked below.

Effect of socioeconomic status in mortality rates after brain injury: cohort study

https://philsf-biostat.github.io/SAR-2023-004-BH/

Sensitivity of mortality rates to the imputation of missing socioeconomic data: cohort study

https://philsf-biostat.github.io/SAR-2023-017-BH/

8.5 Analytical dataset

Table A2 shows the structure of the analytical dataset.

Table A2 *Analytical dataset structure*

id	exposure	outcome	Time	SexF	Race	Mar	AGE	PROBLEMUse	EDUCATION	EMPLOYMENT	RURALdc	PriorSeiz	SCI	Cause	RehabPay1	ResDis	DAYStoREHABdc	FIMMOTD	FIMCOGD	FIMMOTD4	FIMCOGD4
1																					
2																					
3																					
…																					
N																					

Due to confidentiality the data-set used in this analysis cannot be shared online in the public version of this report.