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

DOCUMENT: SAR-2023-016-BH-v01

From: Felipe Figueiredo **To:** Brennan Hickson

2023-12-19

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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 4.3.2.

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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 69,440 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 7,415 participants were included in the analysis.

The epidemiological profile of the participant included in the study was a male participant (5,421 (73%)) with an average (SD) age of 45 (20) years.

Races were not homogeneously available in the study population with 4,941 (67%) individuals being white; 3,170 (43%) were single (never married) at the time of injury, and most participants were well educated with 3,366 (46%) at greater than high school level. A total of 4,378 (59%) were employed and 3,465 (48%) participants lived in an urban area.

Table 1 *Epidemiological, demographic and clinical characteristics of study participants at the time of discharge.*

Characteristic	N = 7,415
SES quintiles, n (%)	
Prosperous	1,353 (22%)
Comfortable	1,239 (20%)
Mid-Tier	1,124 (18%)
At-Risk	1,168 (19%)
Distressed	1,194 (20%)
Missing	1,337
Sex:, n (%)	
Male	5,421 (73%)

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Characteristic	N = 7,415
Female	1,988 (27%)
Missing	6
What is your race?, n (%)	
White	4,941 (67%)
Black	1,144 (15%)
Hispanic	952 (13%)
Other	368 (5.0%)
Missing	10
What is your marital status?, n (%)	
Single (Never Married)	3,170 (43%)
Married	2,595 (35%)
Divorced	921 (12%)
Separated	244 (3.3%)
Widowed	454 (6.1%)
Other	15 (0.2%)
Missing	16
Age at Injury, Mean (SD)	45 (20)
Missing	19

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Characteristic	N = 7,415
Substance Problem Use, n (%)	2,691 (38%)
Missing	264
Education, n (%)	
Greater Than High School	3,366 (46%)
Less Than High School	1,380 (19%)
High School/GED	2,615 (36%)
Missing	54
At time of injury, what was your employment status?, n (%)	
Employed	4,378 (59%)
Unemployed	794 (11%)
Other	2,209 (30%)
Missing	34
Urbanization based on zip code of address at discharge., n (%)	
Suburban	2,192 (30%)
Rural	1,635 (22%)
Urban	3,465 (48%)
Missing	123
Prior to this injury, has a physician ever told you that you have a seizure disorder?, n (%)	52 (5.6%)

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Characteristic	N = 7,415
Missing	6,488
Spinal cord injury:, n (%)	434 (5.9%)
Missing	19
Cause of injury:, n (%)	
Vehicular	3,327 (45%)
Violence	650 (8.8%)
Falls	2,544 (34%)
Other	873 (12%)
Missing	21
Primary rehabilitation payor:, n (%)	
Private Insurance	3,871 (52%)
Public Insurance	2,917 (39%)
Other	600 (8.1%)
Missing	27
Residence after rehab discharge:, n (%)	
Private Residence	5,857 (79%)
Other	1,537 (21%)
Missing	21

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Characteristic	N = 7,415
Days From Injury to Rehab Discharge, Mean (SD)	46 (37)
FIM Motor at Discharge quartiles, n (%)	
Q1	1,856 (25%)
Q2	2,001 (27%)
Q3	1,704 (23%)
Q4	1,747 (24%)
Missing	107
FIM Cognitive at Discharge quartiles, n (%)	
Q1	1,943 (26%)
Q2	1,885 (26%)
Q3	1,827 (25%)
Q4	1,726 (23%)
Missing	34
What is your marital status?, n (%)	
Single	3,170 (43%)
Married	2,595 (35%)
Sep	1,165 (16%)
Other	469 (6.3%)

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Characteristic	N = 7,415
Missing	16
What is your marital status?, n (%)	
Single (Never Married)	3,170 (43%)
Married	2,595 (35%)
Other	1,634 (22%)
Missing	16

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.
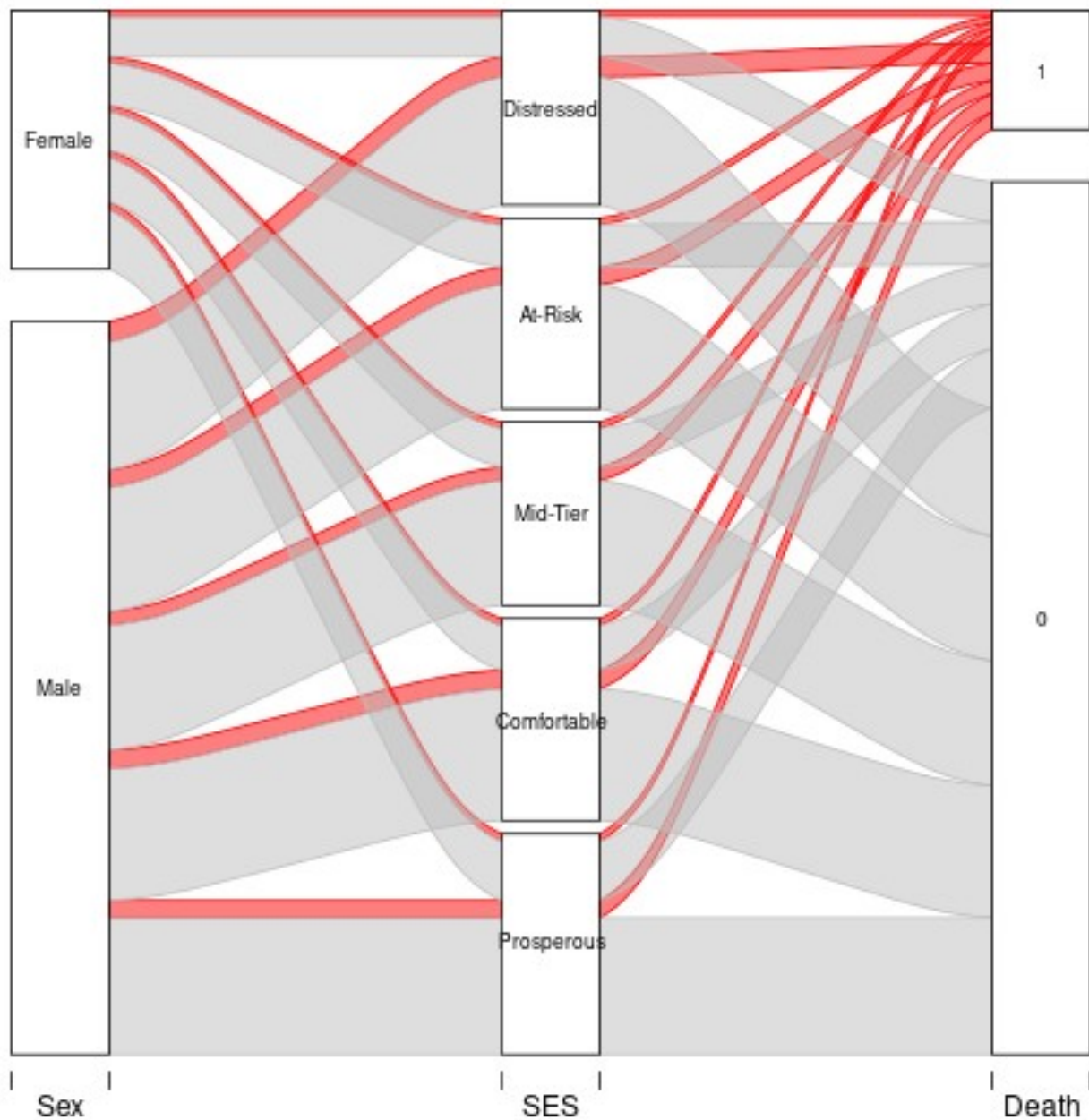
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Figure 1 *Proportion of cases per SES quintiles.*

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4.2   Time-adjusted effect of SES on mortality

Following the findings of **SAR-2023-017-BH-v01** the multiple observations per individual should be favored where the time-varying SES exposure allows the full model specification in this analytical plan to be used. This analysis, however includes an additional model with interactions between the two FIM scores and the exposure that renders those findings obsolete, given that with this new specification all terms satisfy the proportional hazards assumption. This is the model that will be described in this section.

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 5,755 complete cases were available for analysis. The cause of injury   was removed from the model due to violations of the proportional hazards assumption (see section 8.2.1.1.3 in the appendix).

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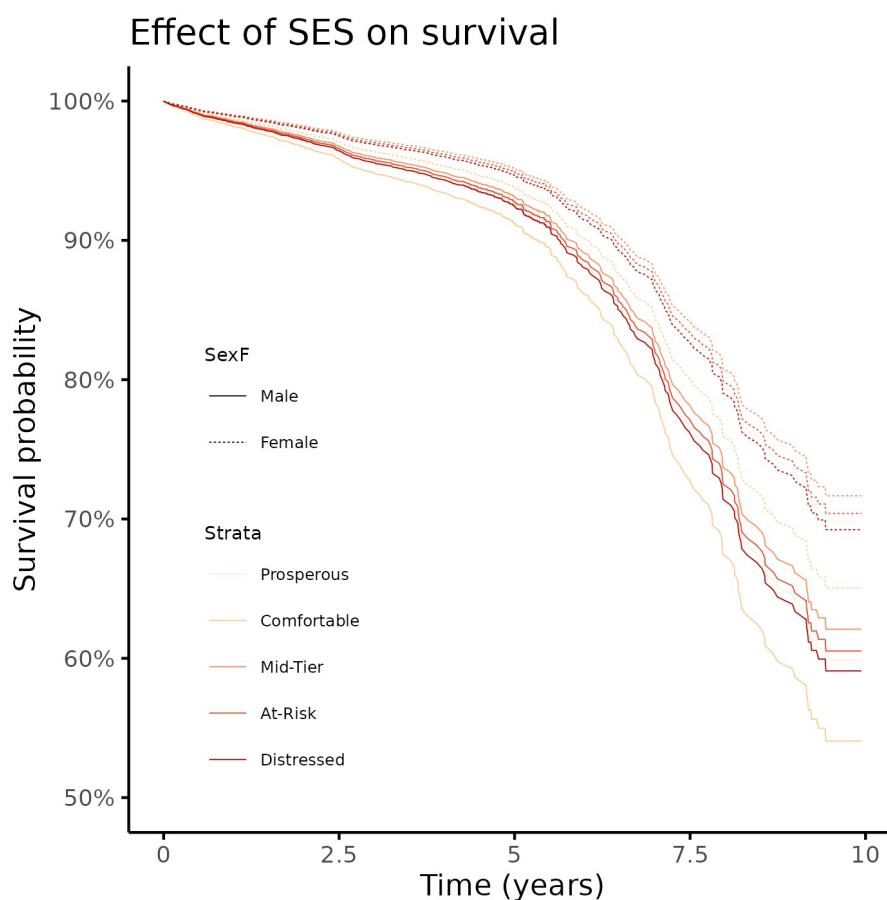
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Figure 2 *Survival of participants, by sex and by SES quintiles.*

The effect of SES of the neighborhood to which the individuals were discharged was associated with mortality and it was modified by the FIM Motor at Discharge quartiles (Table 2). No level of FIM motor function appears to be protective, but participants with the highest functional scores (within the fourth quartile) had a significant increased risk of dying in all neighborhoods, compared to the prosperous neighborhoods.

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Table 2 *Effect of SES on mortality; HR estimates were adjusted for sex, race, age, education, employment status, residence after rehab discharge, urbanization, rehabilitation payer, spinal cord injury, substance abuse, days from injury to rehab, FIM scores quartiles and interactions between FIM scores and the exposure.*

Characteristic	HR[1][2]	95% CI[2]	p-value
SES quintiles			
Prosperous	—	—	
Comfortable	0.78	0.51 to 1.20	0.260
Mid-Tier	0.67	0.42 to 1.08	0.097
At-Risk	0.82	0.53 to 1.27	0.365
Distressed	1.04	0.69 to 1.57	0.841
SES quintiles * FIM Motor at Discharge quartiles			
Comfortable * Q2	1.53	0.84 to 2.77	0.163
Mid-Tier * Q2	1.39	0.73 to 2.65	0.323
At-Risk * Q2	1.20	0.67 to 2.16	0.546
Distressed * Q2	0.98	0.54 to 1.78	0.954
Comfortable * Q3	1.05	0.51 to 2.16	0.884
Mid-Tier * Q3	1.15	0.56 to 2.39	0.706
At-Risk * Q3	1.09	0.54 to 2.20	0.807
Distressed * Q3	1.05	0.54 to 2.04	0.878
Comfortable * Q4	5.19	2.08 to 13.0	**<0.001**

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Characteristic	HR[1][2]	95% CI[2]	p-value
Mid-Tier * Q4	3.59	1.37 to 9.38	**0.009**
At-Risk * Q4	3.41	1.34 to 8.64	**0.010**
Distressed * Q4	5.11	2.06 to 12.7	**<0.001**
SES quintiles * FIM Cognitive at Discharge quartiles			
Comfortable * Q2	0.97	0.52 to 1.82	0.921
Mid-Tier * Q2	1.23	0.63 to 2.42	0.540
At-Risk * Q2	0.86	0.46 to 1.62	0.634
Distressed * Q2	0.79	0.43 to 1.46	0.448
Comfortable * Q3	0.81	0.40 to 1.65	0.564
Mid-Tier * Q3	2.12	1.02 to 4.41	**0.043**
At-Risk * Q3	1.30	0.67 to 2.54	0.444
Distressed * Q3	1.05	0.53 to 2.04	0.896
Comfortable * Q4	0.76	0.36 to 1.60	0.468
Mid-Tier * Q4	0.90	0.39 to 2.08	0.809
At-Risk * Q4	1.88	0.89 to 3.99	0.100
Distressed * Q4	0.93	0.44 to 1.97	0.845

[1]Adjusted by demographic + geographical + clinical variables + FIM scores + Interactions

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

Additionally it appears that the risk of dying associated with the DCI in neighborhoods has a "U-shape", where "comfortable" and "distressed" locations show a higher incidence

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than both "mid-tier" and "at-risk" locations. This might indicate a more complex non-linear relationship between SES and FIM scores that could be evaluated in future studies.

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 a 31 years old white male, that has greater than high school level of education, is actively employed and lives in an urban setting.

After controlling for demographic, geographical, clinical variables and FIM scores SES is associated with an increased incidence of mortality when participants also have higher levels of motor function. This association holds regardless of what neighborhood participants were discharged to.

7   REFERENCES
- **SAP-2023-016-BH-v03** – Analytical Plan for Time-adjusted effect of socioeconomic status in mortality rates after brain injury: cohort study
- **SAR-2023-017-BH-v01** – Sensitivity of mortality rates to the imputation of missing socioeconomic data: 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).

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8 APPENDIX

8.1 Exploratory data analysis
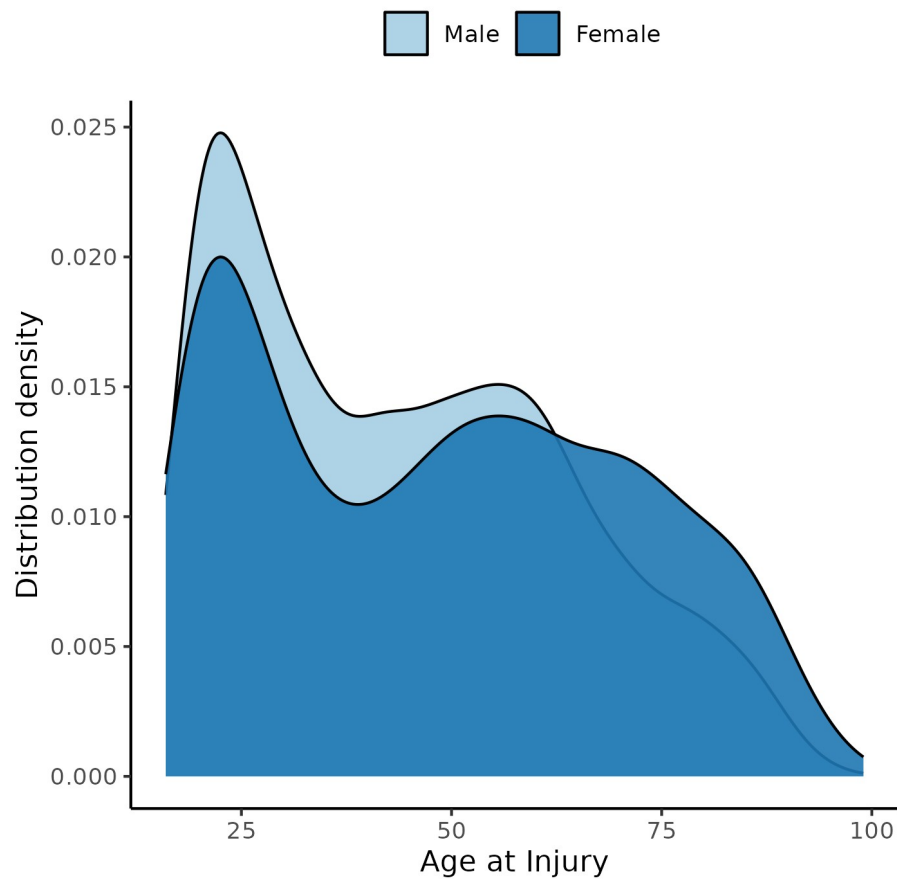
Figure A1 *Distribution of age in the study population.*

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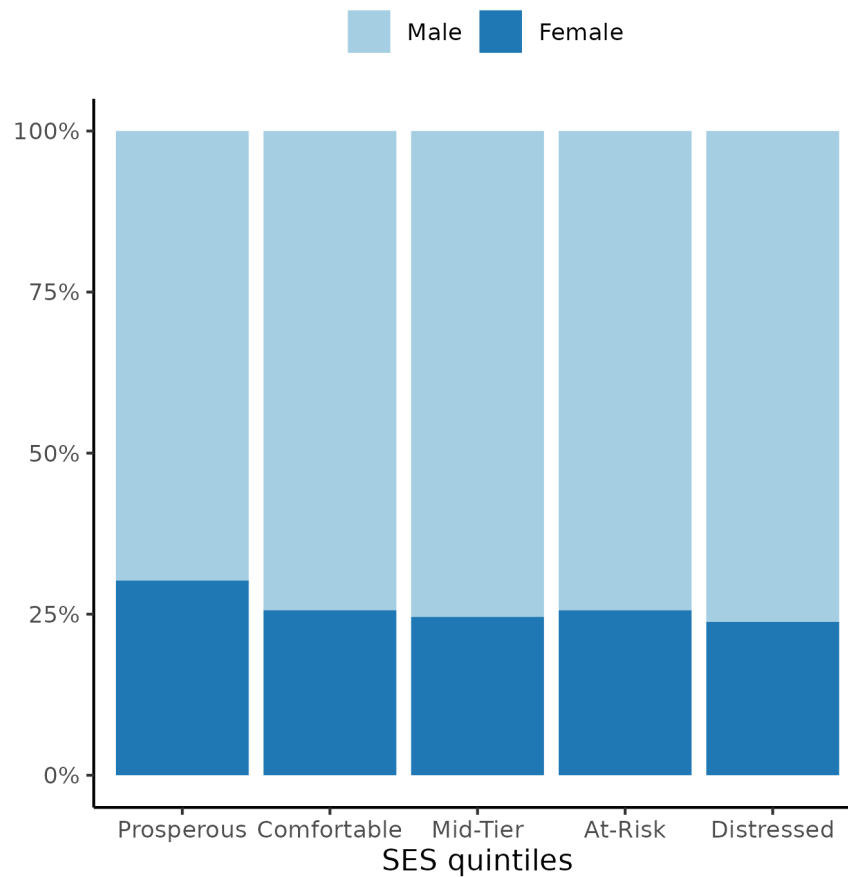
Figure A2 *Distribution of SES in the study population.*

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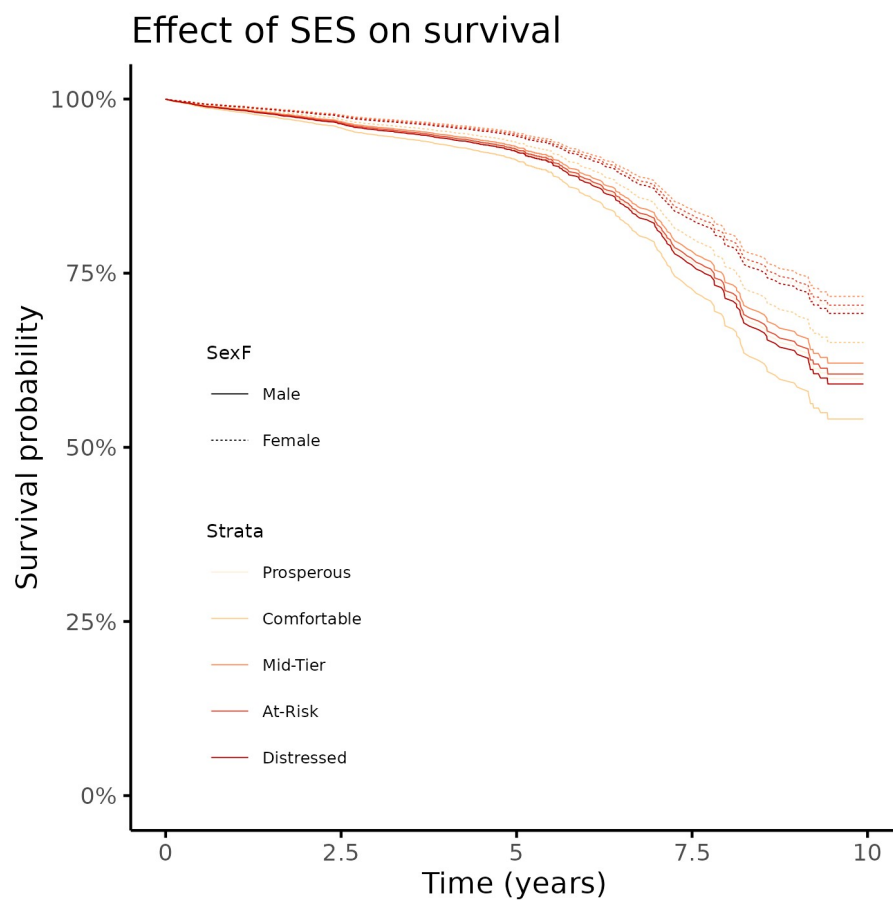
Figure A3 *Alternative version of figure 2.*

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8.2   Modeling strategy

8.2.1 Approaches to control for time-dependent covariates

8.2.1.1   Before location/SES imputation

Imputation was done in a separate analysis and is described in the report **SAR-2023-017-v01**.

8.2.1.1.1   Schoenfeld and Martingale residuals
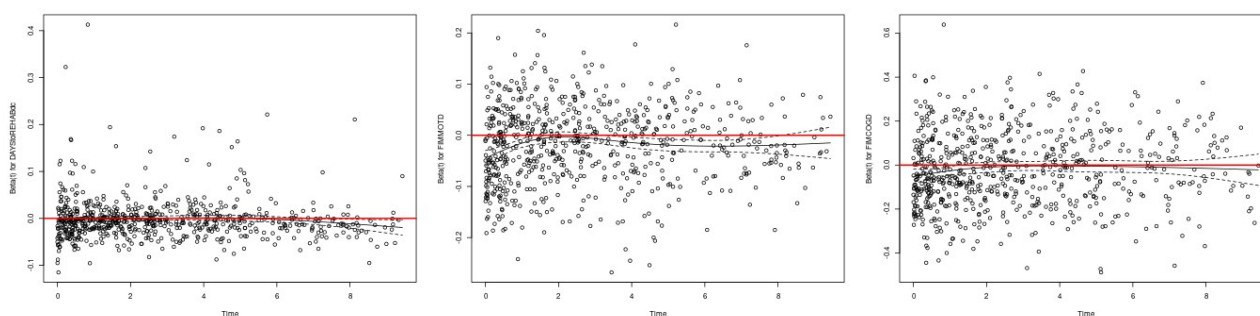

Figure A4 *caption*

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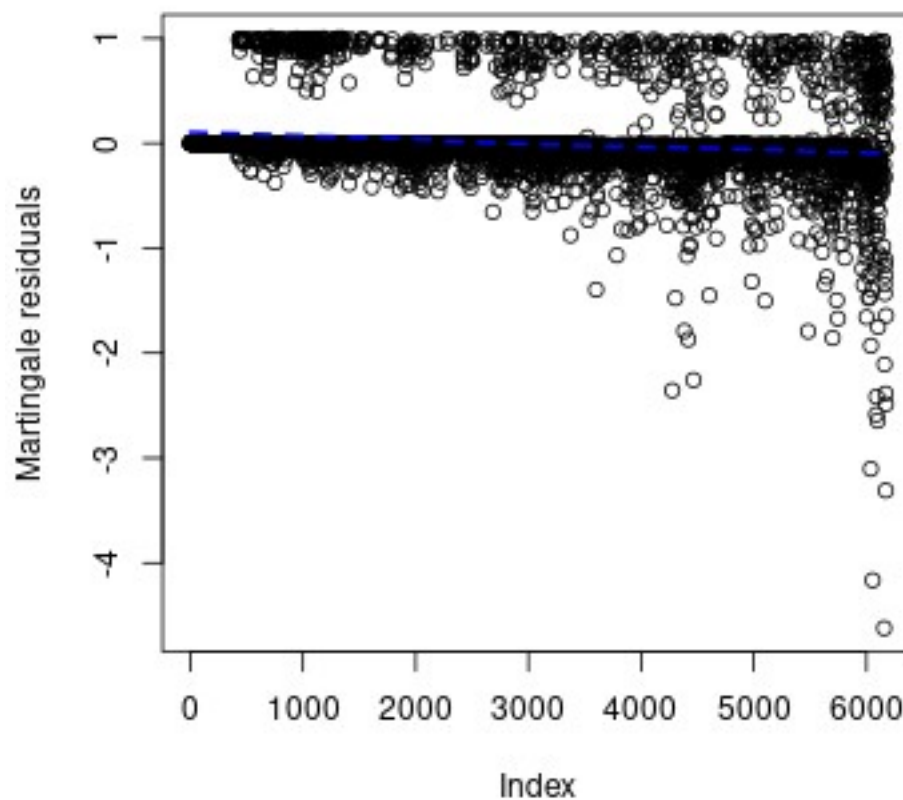| Version	Year	Page
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Figure A5 caption

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)

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8.2.1.1.2   Martingale residuals of covariates against the null model
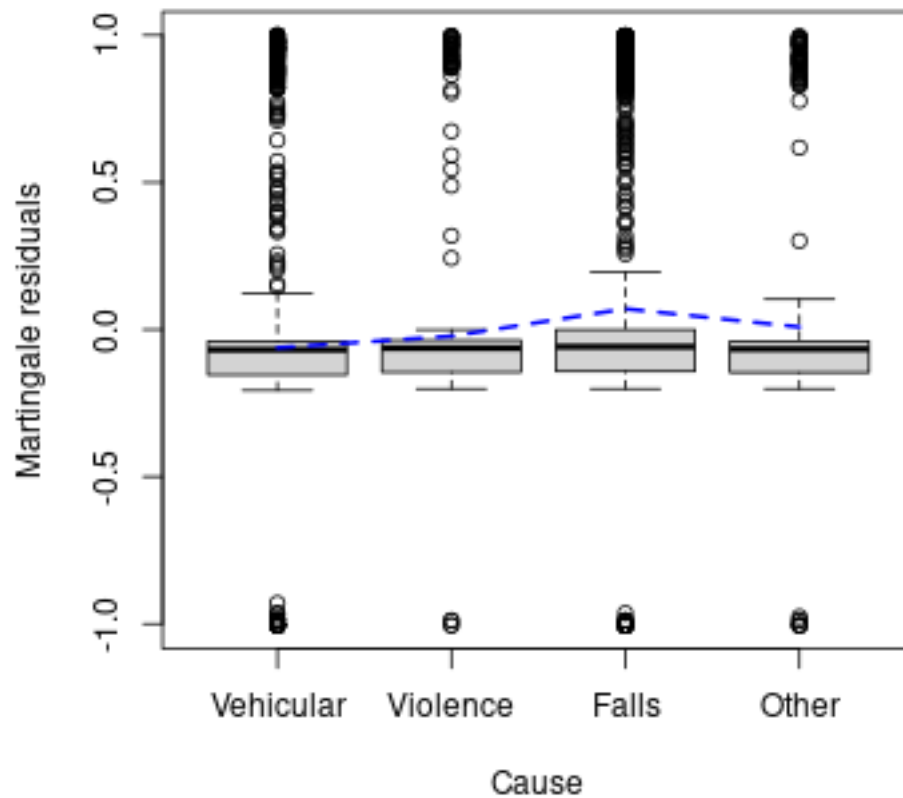
Figure A6 caption

Figure A7 caption

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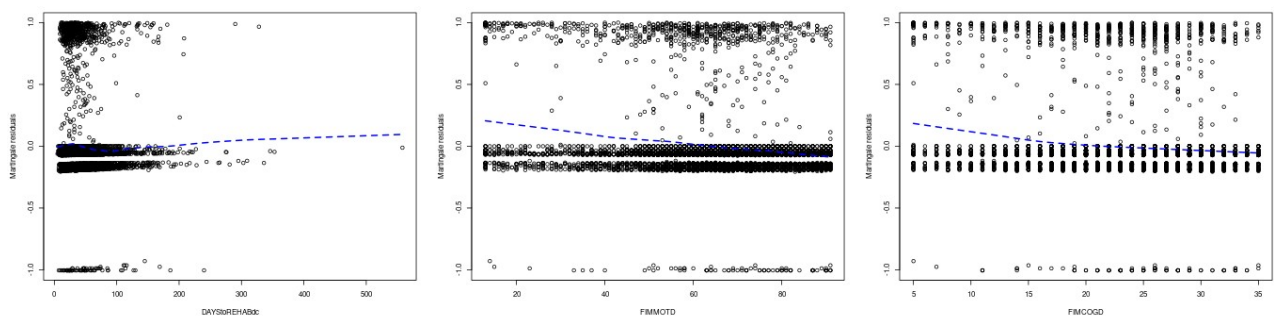
Notes:

- 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)

8.2.1.1.3   Stratification by cause of injury

Figure A8 caption

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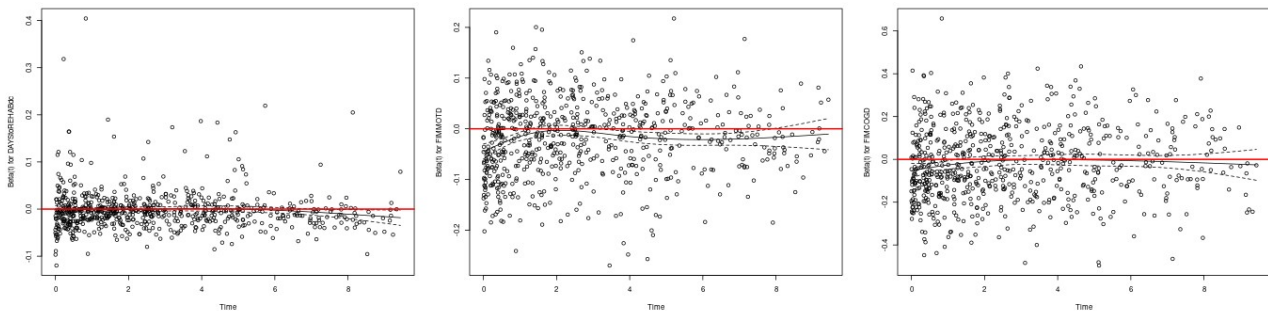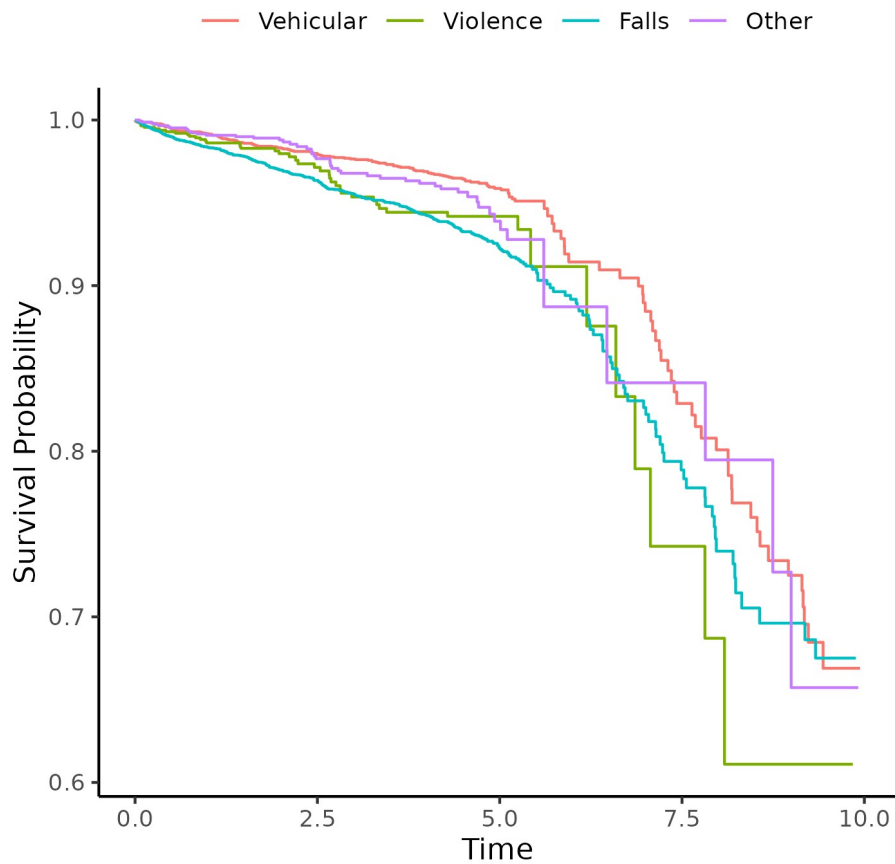
Figure A9 *caption*

Notes:

- stratifying by cause appears to help with non-PH of the 3 vars (A8)
- cause violates the PH assumption (A9)

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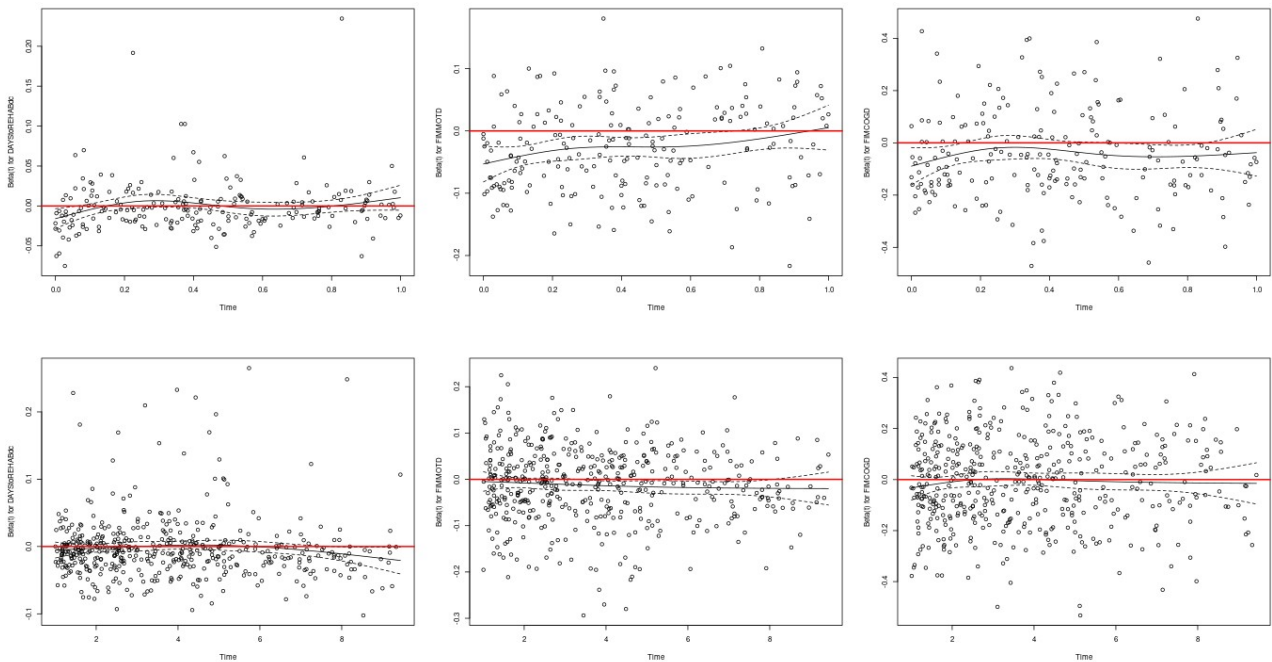
8.2.1.1.4   Time split

Figure A10 caption

Notes:

- time split at 1yr doesn't help further (A10)

8.2.1.1.5   Non-linear fitting

Figure A11 caption

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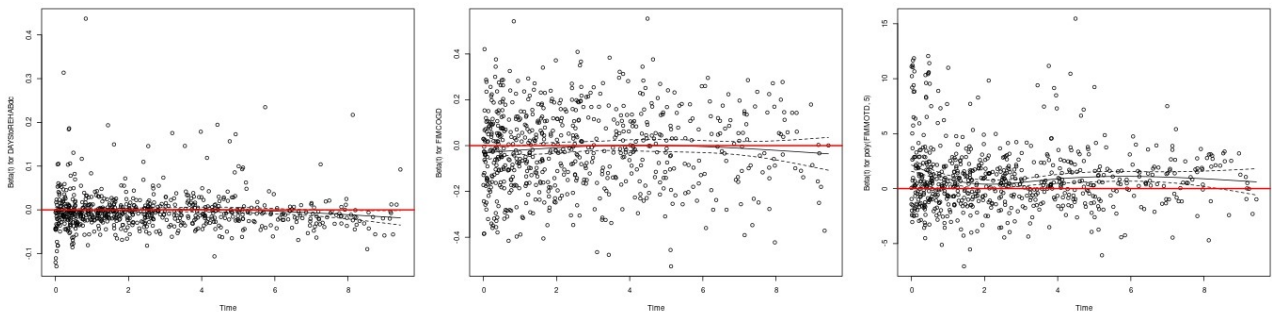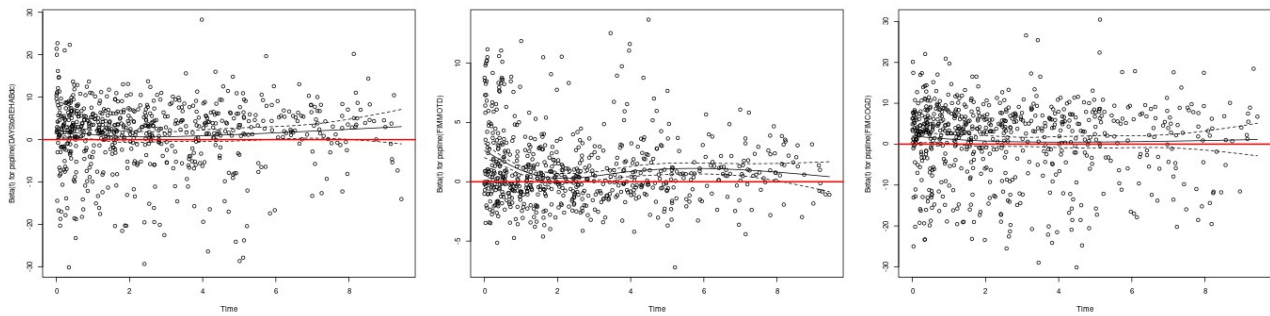
Figure A12 *caption*

Notes:

- polynomials (A11) and splines (A12) appear to help stabilize residuals, but not enough

8.2.1.1.6   Interaction with time
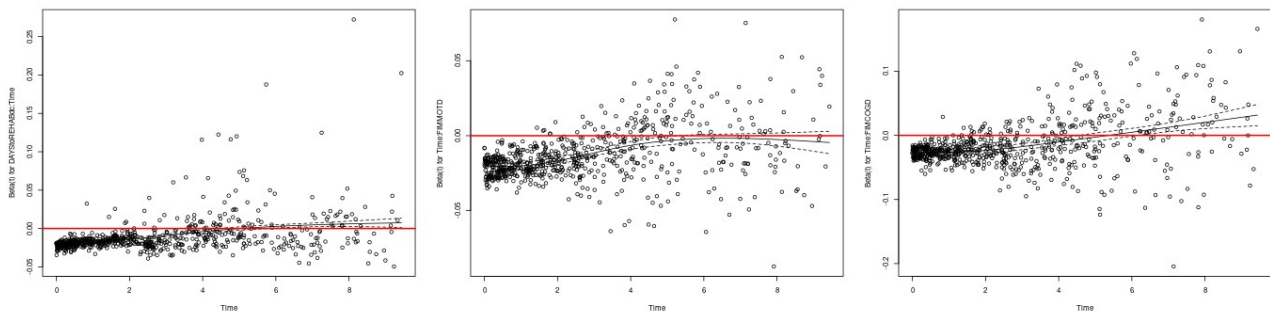
Figure A13 *caption*

Notes:

- makes non-PH worse, not helpful at all (A13)

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8.2.1.1.7   FIM scores quartiles
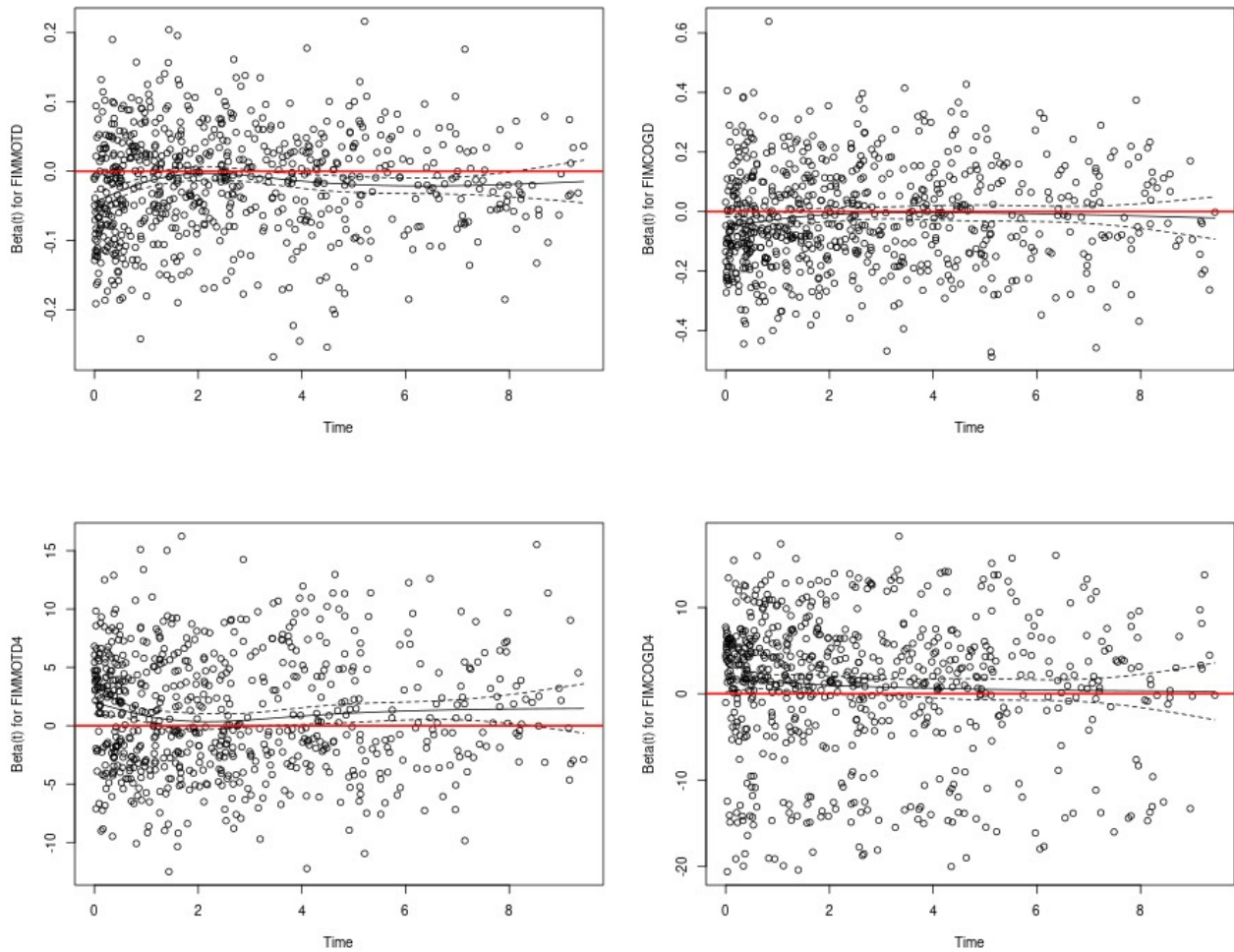
Figure A14 *caption*

Notes:

- days still non-PH (A14)
- FIM scores seem PH enough (A14)

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8.2.1.2 Best model specification

Figure A15 *caption*

Notes:

- removing days makes residuals appear PH (A15)
- passes schoenfeld test
- final model: strat by cause + FIM quartiles + drop days

8.2.1.3 After location/SES imputation

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8.2.2 Schoenfeld test
Table A1 *P-values of the Schoenfeld test for all 6 models.*

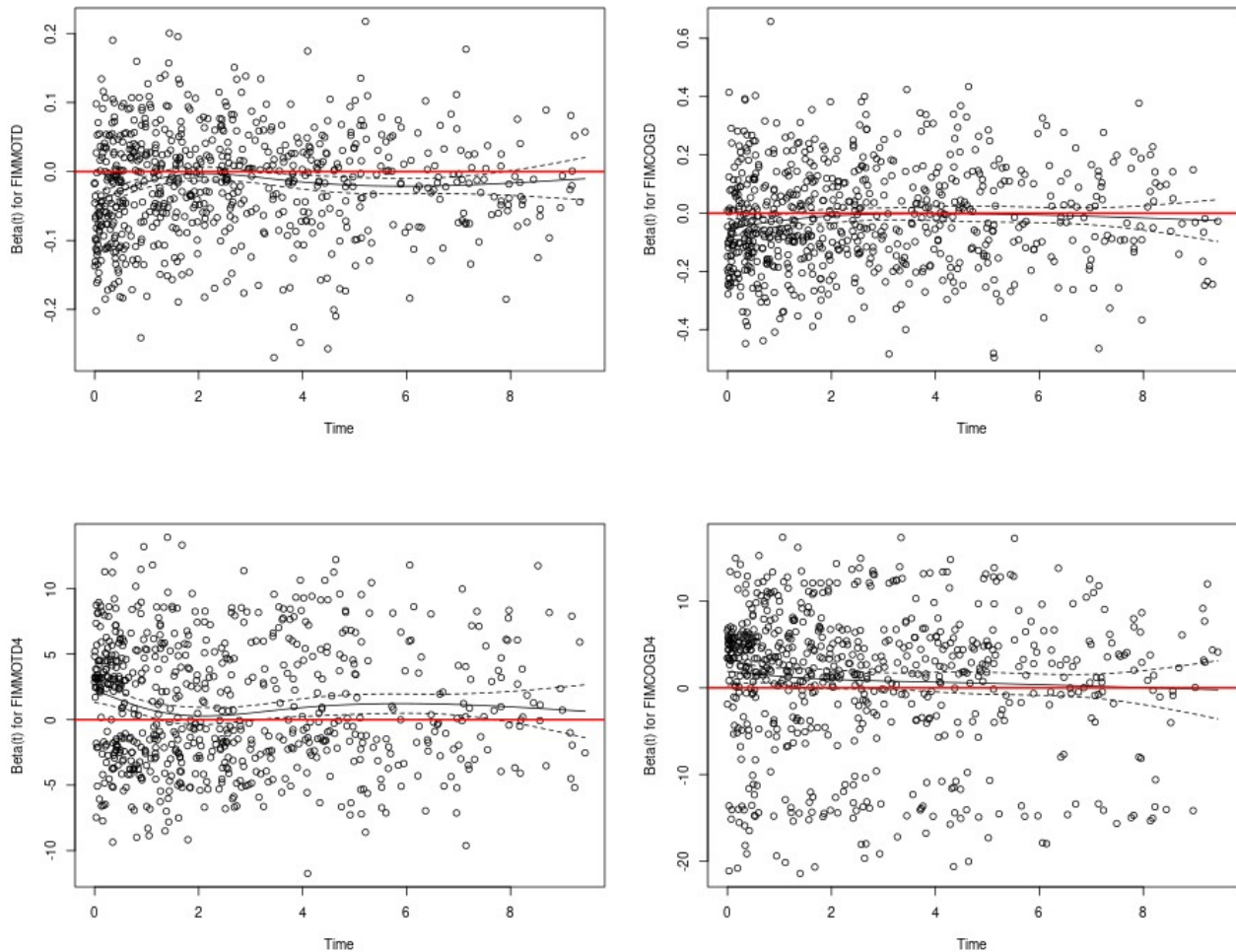| term	model1	model2	model3	model4	model5	model6
exposure	0.062	0.6	0.7	0.6	0.5	0.6
GLOBAL	0.062	0.3	0.3	0.6	0.2	0.3
SexF	NA	0.051	0.12	0.2	0.2	0.13
Race	NA	0.12	0.12	0.2	0.3	0.3
AGE	NA	0.13	0.3	0.5	0.7	0.9
EDUCATION	NA	>0.9	>0.9	0.9	>0.9	>0.9
EMPLOYMENT	NA	0.072	0.10	0.2	0.3	0.3
ResDis	NA	NA	0.2	0.3	0.4	0.5
RURALdc	NA	NA	0.14	0.3	0.3	0.3
RehabPay1	NA	NA	NA	0.5	0.6	0.6
SCI	NA	NA	NA	0.4	0.3	0.14
PROBLEMUse	NA	NA	NA	0.4	0.4	0.4
DAYStoREHABdc	NA	NA	NA	0.2	0.052	0.071
FIMMOTD4	NA	NA	NA	NA	0.045	0.12
FIMCOGD4	NA	NA	NA	NA	0.2	0.14
exposure:FIMMOTD4	NA	NA	NA	NA	NA	0.088
exposure:FIMCOGD4	NA	NA	NA	NA	NA	0.3

8.2.3 Final model specification

Table A2 *Alternative version of Table 2, showing the coefficients from all covariates included in all 6 models.*

	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Characteristic	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]	**HR (SE)**[12]
SES quintiles						
Prosperous	—	—	—	—	—	—
Comfortable	1.16 (0.118)	1.06 (0.118)	0.97 (0.121)	0.97 (0.121)	0.97 (0.121)	0.78 (0.216)
Mid-Tier	0.98 (0.125)	1.16 (0.126)	1.12 (0.129)	1.12 (0.129)	1.08 (0.130)	0.67 (0.242)
At-Risk	1.28* (0.120)	1.30* (0.121)	1.19 (0.125)	1.17 (0.125)	1.10 (0.126)	0.82 (0.225)
Distressed	1.33* (0.116)	1.37* (0.123)	1.32* (0.126)	1.30* (0.127)	1.20 (0.127)	1.04 (0.209)
Sex:						

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Characteristic	Model 1 HR (SE)[1][2]	Model 2 HR (SE)[1][2]	Model 3 HR (SE)[1][2]	Model 4 HR (SE)[1][2]	Model 5 HR (SE)[1][2]	Model 6 HR (SE)[1][2]
Male		—	—	—	—	—
Female		0.64*** (0.088)	0.64*** (0.088)	0.67*** (0.089)	0.70*** (0.089)	0.70*** (0.090)
What is your race?						
White		—	—	—	—	—
Black		0.83 (0.116)	0.81 (0.119)	0.81 (0.119)	0.81 (0.120)	0.81 (0.120)
Hispanic		0.64** (0.162)	0.61** (0.167)	0.61** (0.168)	0.59** (0.168)	0.56*** (0.169)
Other		0.73 (0.206)	0.73 (0.207)	0.72 (0.207)	0.71 (0.208)	0.68 (0.210)
Age at Injury		1.04*** (0.002)	1.04*** (0.002)	1.04*** (0.003)	1.04*** (0.003)	1.04*** (0.003)
Education						
Greater Than High School		—	—	—	—	—
Less Than High School		1.21 (0.114)	1.25 (0.114)	1.23 (0.115)	1.17 (0.115)	1.21 (0.117)
High School/GED		1.39*** (0.087)	1.39*** (0.088)	1.37*** (0.088)	1.36*** (0.088)	1.35*** (0.089)
At time of injury, what was your employment status?						
Employed		—	—	—	—	—
Unemployed		2.22*** (0.136)	2.13*** (0.137)	1.82*** (0.142)	1.75*** (0.142)	1.78*** (0.143)
Other		2.21*** (0.100)	2.16*** (0.100)	2.01*** (0.105)	1.81*** (0.106)	1.83*** (0.107)
Residence after rehab discharge:						

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Characteristic	Model 1 HR (SE)[12]	Model 2 HR (SE)[12]	Model 3 HR (SE)[12]	Model 4 HR (SE)[12]	Model 5 HR (SE)[12]	Model 6 HR (SE)[12]
Private Residence			—	—	—	—
Other			1.77*** (0.083)	1.70*** (0.085)	1.44*** (0.088)	1.42*** (0.089)
Urbanization based on zip code of address at discharge.						
Suburban			—	—	—	—
Rural			1.00 (0.115)	1.01 (0.115)	1.03 (0.116)	1.01 (0.117)
Urban			1.13 (0.095)	1.08 (0.096)	1.13 (0.096)	1.15 (0.097)
Primary rehabilitation payor:						
Private Insurance				—	—	—
Public Insurance				1.41*** (0.095)	1.38*** (0.095)	1.39*** (0.095)
Other				1.16 (0.185)	1.10 (0.185)	1.09 (0.186)
Spinal cord injury:				1.21 (0.175)	1.29 (0.176)	1.26 (0.178)
Substance Problem Use				1.22* (0.093)	1.27** (0.094)	1.30** (0.095)
Days From Injury to Rehab Discharge				1.00* (0.001)	1.00 (0.001)	1.00 (0.001)
FIM Motor at Discharge quartiles						
Q1					—	—
Q2					0.67*** (0.102)	0.56** (0.215)
Q3					0.65*** (0.122)	0.60* (0.247)

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Characteristic	Model 1 HR (SE)[1][2]	Model 2 HR (SE)[1][2]	Model 3 HR (SE)[1][2]	Model 4 HR (SE)[1][2]	Model 5 HR (SE)[1][2]	Model 6 HR (SE)[1][2]
Q4					0.55*** (0.143)	0.17*** (0.379)
FIM Cognitive at Discharge quartiles						
Q1					—	—
Q2					0.84 (0.105)	0.89 (0.219)
Q3					0.81 (0.111)	0.70 (0.253)
Q4					0.64*** (0.128)	0.65 (0.273)
SES quintiles * FIM Motor at Discharge quartiles						
Comfortable * Q2						1.53 (0.303)
Mid-Tier * Q2						1.39 (0.331)
At-Risk * Q2						1.20 (0.300)
Distressed * Q2						0.98 (0.303)
Comfortable * Q3						1.05 (0.366)
Mid-Tier * Q3						1.15 (0.372)
At-Risk * Q3						1.09 (0.358)
Distressed * Q3						1.05 (0.338)
Comfortable * Q4						5.19*** (0.467)
Mid-Tier * Q4						3.59** (0.490)

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Statistical Analysis Report (SAR)

Characteristic	Model 1 HR (SE)[1][2]	Model 2 HR (SE)[1][2]	Model 3 HR (SE)[1][2]	Model 4 HR (SE)[1][2]	Model 5 HR (SE)[1][2]	Model 6 HR (SE)[1][2]
At-Risk * Q4						3.41** (0.475)
Distressed * Q4						5.11*** (0.463)
SES quintiles * FIM Cognitive at Discharge quartiles						
Comfortable * Q2						0.97 (0.322)
Mid-Tier * Q2						1.23 (0.343)
At-Risk * Q2						0.86 (0.323)
Distressed * Q2						0.79 (0.313)
Comfortable * Q3						0.81 (0.361)
Mid-Tier * Q3						2.12* (0.373)
At-Risk * Q3						1.30 (0.342)
Distressed * Q3						1.05 (0.342)
Comfortable * Q4						0.76 (0.382)
Mid-Tier * Q4						0.90 (0.427)
At-Risk * Q4						1.88 (0.384)
Distressed * Q4						0.93 (0.384)

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

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

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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 A3 shows the structure of the analytical dataset.

Table A3 *Analytical dataset structure*

id	exposure	outcome	Time	SexF	Race	Mar	AGE	PROBLEMUse	EDUCATION	EMPLOYMENT	RURALdc	PriorSeiz	SCI	Cause	RehabPay1	ResDis	DAYStoREHABdc	FIMMOTD	FIMCOGD	FollowUp Period	FIMMOT D4	FIMCOG D4	Mar2	Mar3
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.

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