Cox Proportional Hazard Regression and Splines: A Cautionary Tale for exposure-response assessment

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Outline:

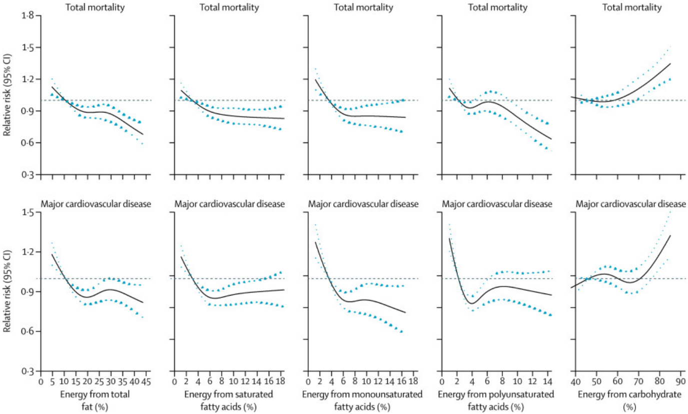
- Splines and Cox Regression
- Exposure-Response Examples
- Simulation
- Conclusions

- Splines are functions that are used to “smooth” continuous measurements
- Can be thought of as polynomials
- A set of *knots* are selected and polynomial functions are calculated between each knot and are independent of the shape between previous knots
- Two popular types of splines are Restricted Cubic Splines (RCS) (Durrleman and Simon 1989) and Penalized Splines (PS) (Eilers and Marx 1996)
- RCS restricts the shape to linear below the first knot and past the last knot while PS forces the parameters to be “close” to each other

- Cox proportional hazards models are used to estimate hazard ratios for certain events
- Used for time-to-event outcomes, such as death or disease onset

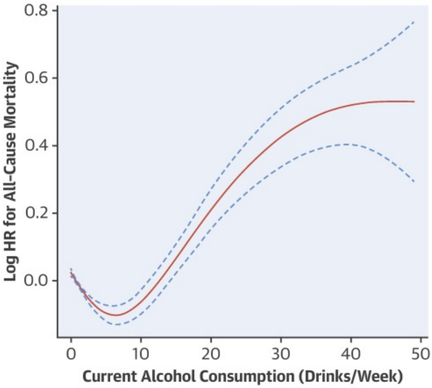
- Splines and Cox regression are frequently used together when analyzing time to event data with continuous exposures
- As they make minimal assumptions, an analysis based upon these combined approaches is often thought to be robust to model mis-specification
- We were interested in how robust

Miller et al. 2017



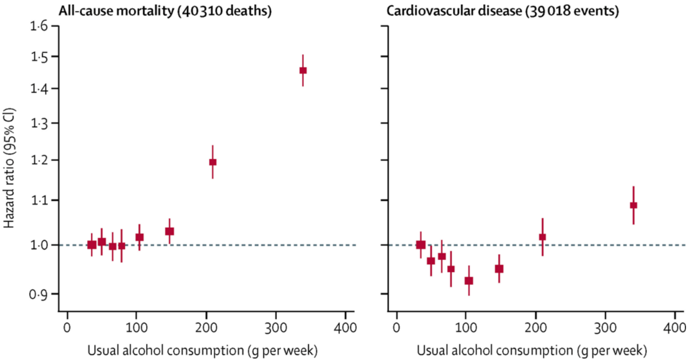
- In many public health studies of the effects of alcohol on various outcomes, frequently cardiovascular outcomes, have observed that a small amount of alcohol consumption can be protective
- A small sample include Chokshi 2015, Di Castelnuova 2006, and Xi et al. 2017

CENTRAL ILLUSTRATION: Alcohol Consumption and All-Cause Mortality Risk in U.S. Adults



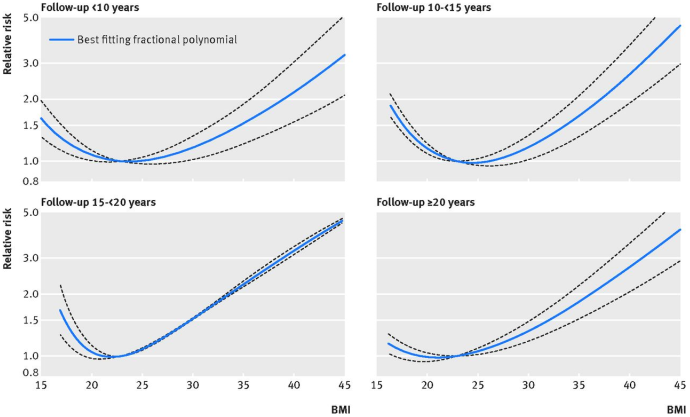
Xi, B. et al. J Am Coll Cardiol. 2017;70(8):913-22.

- A recent analysis of individual-participant data of three large data sets (Emerging Risk Factors Collaboration, EPIC-CVD, and the UK Biobank) examined the relationship between alcohol and CVD outcomes (Wood et al. 2018)
- “The chief implication for scientific understanding is that ... the association between alcohol consumption and total cardiovascular disease risk is actually comprised of several distinct and opposite dose-response curves rather than a single J-shaped association”


All-cause mortality (40 310 deaths)
Cardiovascular disease (39 018 events)
Hazard ratio (95% CI)
1·6
1·5
1·4
1·3
1·2
1·1
1·0
0·9
0
100
200
300
400
Usual alcohol consumption (g per week)
Usual alcohol consumption (g per week)

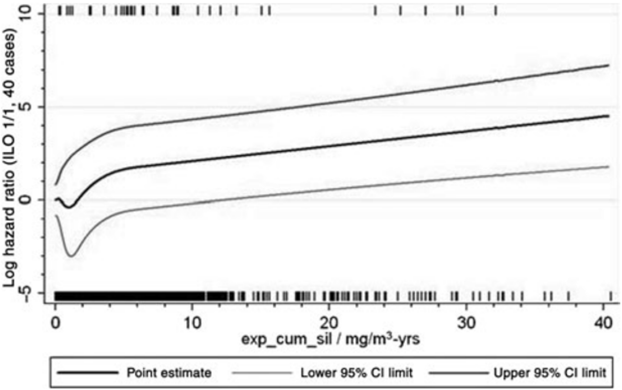
- Such an J-curves can be termed as a hormetic effect, and has been observed in different settings:
- Cancer caused by Radon/radiation exposure (Thompson 2011 and Nakashima 2015)
- BMI and all cause mortality (Aune et al 2016)
- A database of hormetic dose responses (Calabrese and Blain, 2011) included 2527 citations across various exposures and outcomes

Non-linear dose-response analysis of BMI and all cause mortality in never smokers stratified by duration of follow-up, Aune et al. 2016

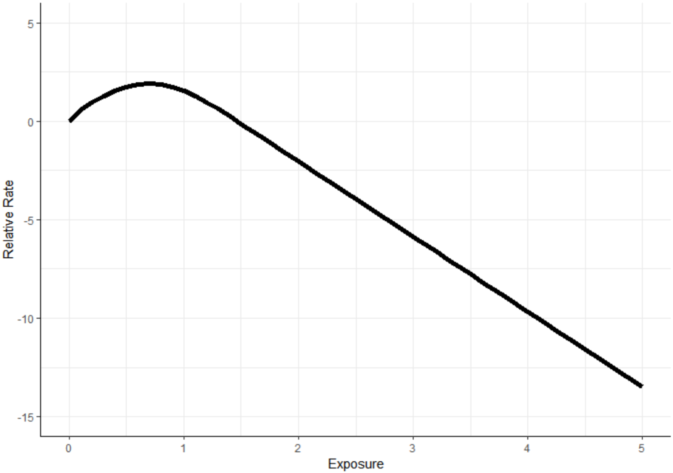


- J-curves are often observed when using the Cox model with spline models
- Is this a coincidence?
- Are these relationships truly present or are they an artifact of the modeling choices and exposure distribution?

- Silicosis is a form of pneumoconiosis, a dust-induced lung disease, resulting from inhalation of silica (Park and Chen 2013)
- It ONLY occurs when there is silica exposure.
- While not significant nor highlighted by the authors, a J-shape curve was seen in an analysis of a large cohort study (Morfeld et al. 2013)


Log hazard ratio (ILO 1/1, 40 cases)
10
5
0
-5
0
10
20
30
40
exp_cum_sil / mg/m³-yrs
Point estimate
Lower 95% CI limit
Upper 95% CI limit

- Another study of 2862 tin miners was performed by Park and Chen (2013) and did not observe a J-shaped relationship
- However, they did not perform Cox proportional hazard regression nor use splines
- What would be seen if they had?


5
0
-5
-10
-15
Relative Rate
0
1
2
3
4
5
Exposure

- This illustrates that with a poor choice of knots in RCS we can observe a non-monotone incorrect relationship
- A J-shaped curve may be a mathematical side effect of combining a spline model and a Cox model.

- Consider a model with exposure X and outcome Y
  - Y_i is the observed time for subject i with event indicator C_i
  - X_i be a non-negative exposure for subject i.
  - $b_k(x)$ represent the k^{th} spline basis function for X defined over a knot set $\mathcal{T}$

- Let $f(x) = \sum_{k=1}^{K} \beta_k b_k(x)$ be some function we wish to estimate using the spline basis, where β_k are unknown coefficients
- Without too much loss of generality, assume our spline basis is monotone, such that $f(x)$ is decreasing when $\beta_k < 0$ and increasing when $\beta_k > 0$
- To observe a J-shaped response, it is necessary that the first derivative be negative and then positive; that is, the initial β_k coefficients need to be negative and then positive.
- For maximum likelihood estimation, it is sufficient to investigate the score function for the Cox proportional hazards model when $b_k(x)$ is a monotone spline.

- Define $f(x)$ as above and consider the score function of Cox proportional hazard

$$\dot{\ell}(\beta_k) = \sum_{i=1}^{n} \left[b_k(x_i)\, 1_{\{C_i=1\}} + \frac{\sum_{j=1}^{n} \theta_j b_k(x_j)\, 1_{\{Y_j > Y_i\}}}{\sum_{j=1}^{n} \theta_j\, 1_{\{Y_j > Y_i\}}} \right], \qquad (1)$$

  where $1_{\{\cdot\}}$ is 1 if the logical condition is satisfied, zero otherwise, and $\theta_j = \exp(\sum_{k=1}^{K} \beta_k b_k(x_j))$.
- To have a non-monotone curve, it a necessary condition for $\beta_k < 0$, for some k.

- For any β_k to be less than 0, it is a necessary condition for the mean of (1) this quantity to be negative at $\beta_k = 0$

$$\frac{1}{n}\sum_{i=1}^{n}\left[b_k(x_i)\,1_{\{C_i=1\}} + \frac{\sum_{j=1}^{n} b_k(x_j)\,1_{\{Y_j>Y_i\}}}{\sum_{j=1}^{n}\,1_{\{Y_j>Y_i\}}}\right] < 0, \qquad (2)$$

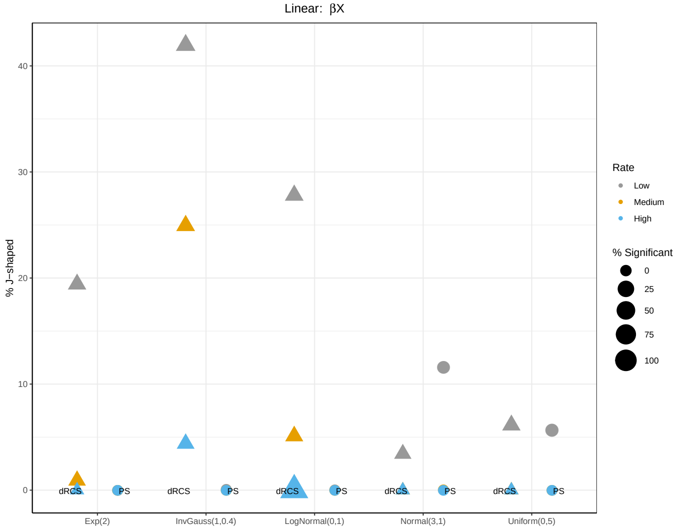
where $\theta_j = 1$ because $\beta_k = 0$ for all k.

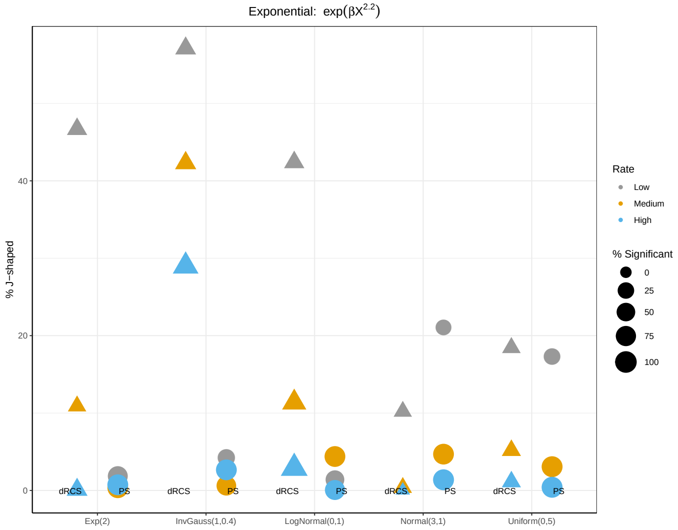
- For large n this quantity converges almost surely and is dependent on the expectation of $E[b_k(x_i)\,1_{C_i=1}]$, which is solely dependent on the distribution of the exposure and the chosen spline basis.

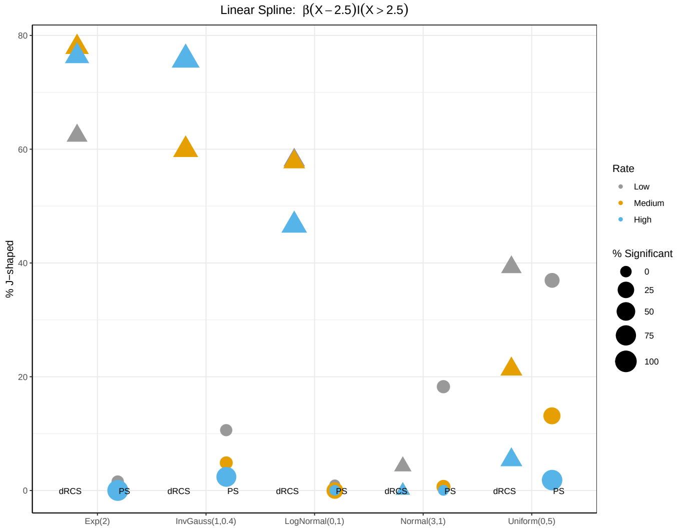
- Thus, the presence of a J-shape, or other non-monotone shape, when the **true** relationship is monotone, depends on the exposure distribution
- The exposure distribution is typically uncontrollable by the researcher
- What scenarios, that is exposures, spline bases, exposure-response relationships, would be likely to create a “false” J-shape?

- To investigate the magnitude of J-curves in these splines a simulation study was performed
- Conditions for simulation were selected using the data from Park and Chen (2013)
- Silica exposures were generated from 4 distributions:
  - Exponential (EXP)(mean=2)
  - Inverse Gausian (IG)(mean=1, shape=0.4)
  - LogNormal (LOG)(0,1)
  - Normal(mean=3, standard deviation=1)
  - Uniform (U)(0,5)
- RCS with 6 knots and PS were allowed to estimate knots naturally

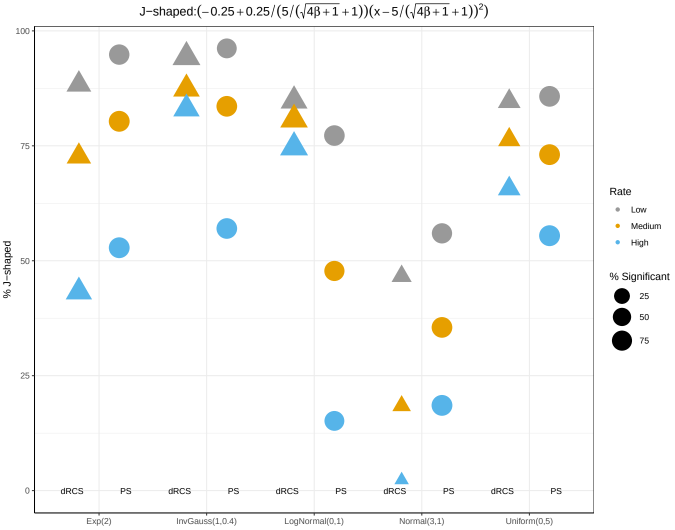
- Generate data for 1,000, 5,000 and 15,000 subjects
- Event times generated from 4 types of non-decreasing response rates with 3 rates each
  - Exponential
  - Linear
  - Linear Spline, “Hockey stick”
  - J-shape
- Presence of J-shape relationships were recorded and, if found, tested for significance using Wald based Z-tests

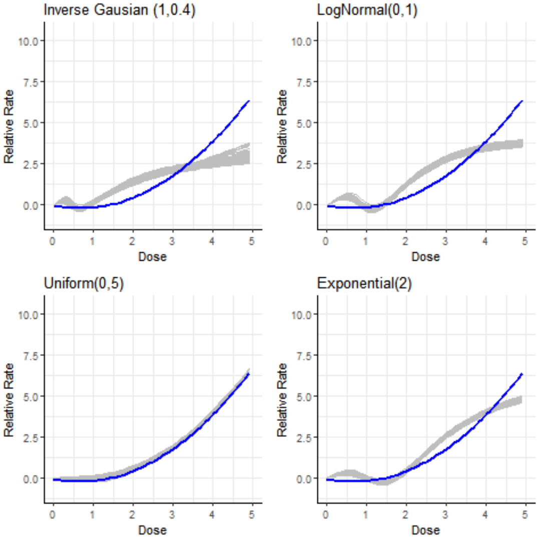

Linear: βX
% J−shaped
0
10
20
30
40
dRCS
PS
Exp(2)
InvGauss(1,0.4)
LogNormal(0,1)
Normal(3,1)
Uniform(0,5)
Rate
Low
Medium
High
% Significant
0
25
50
75
100

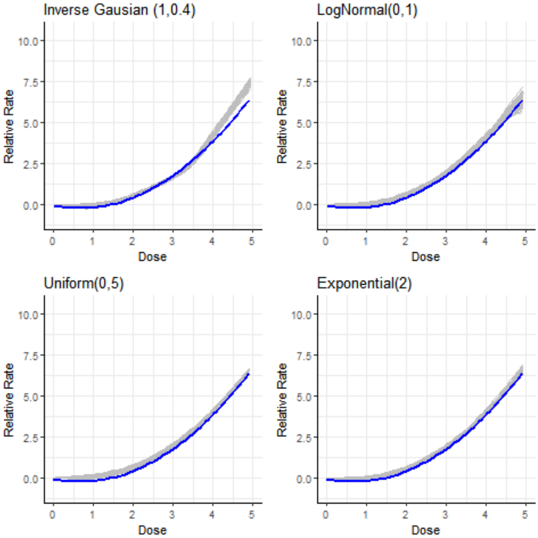

Exponential: exp(βX^2.2)
% J−shaped
0
20
40
dRCS
PS
Exp(2)
InvGauss(1,0.4)
LogNormal(0,1)
Normal(3,1)
Uniform(0,5)
Rate
Low
Medium
High
% Significant
0
25
50
75
100



Linear Spline: β(X − 2.5)I(X > 2.5)
% J−shaped
80
60
40
20
0
dRCS
PS
Exp(2)
InvGauss(1,0.4)
LogNormal(0,1)
Normal(3,1)
Uniform(0,5)
Rate
Low
Medium
High
% Significant
0
25
50
75
100


J−shaped:(−0.25+0.25/(5/(√4β+1+1))(x−5/(√4β+1+1))^2)
% J−shaped
100
75
50
25
0
dRCS
PS
dRCS
PS
dRCS
PS
dRCS
PS
dRCS
PS
Exp(2)
InvGauss(1,0.4)
LogNormal(0,1)
Normal(3,1)
Uniform(0,5)
Rate
Low
Medium
High
% Significant
25
50
75


Inverse Gausian (1,0.4)
LogNormal(0,1)
Uniform(0,5)
Exponential(2)
Relative Rate
Dose
10.0
7.5
5.0
2.5
0.0
0
1
2
3
4
5


Inverse Gausian (1,0.4)
LogNormal(0,1)
Uniform(0,5)
Exponential(2)
Relative Rate
Dose
10.0
7.5
5.0
2.5
0.0
0
1
2
3
4
5

- Very high rate of J-shapes curves
- Statistically significant relationships present in a high percentage of simulations
- Other non-monotone, biased, relationships were observed but not captured

- Using polynomial splines within Cox regression is a common practice
- J-shape curves could be observed even if that shape is not true depending on the exposure distribution
- We are ***not*** suggesting that spline models are bad, nor that J-shaped relationships do not exist in nature, just that cautious examination should be given to any analysis where the J-shape appears

- Model averaging technique that provides unbiased estimates independent of exposure distribution
- Other non-monotone shapes
- Characterization of likelihood for incorrectly estimated non-monotone relationships, i.e. can more information about shape be hidden in the combination of the stochastic Cox proportional hazards model and the spline basis

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