-EMC-, Visualizing effect modifications

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Background

In Bernard et al. (1997) it was analysed whether treatment with ibuprofen on patients with blood poisoning (sepsis)

1. Did improve 30 days survival?
2. Did decrease fewer?

It was found that ibuprofen did not improve survival, but it did decrease fewer...

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Questions

1. At baseline a severity-of-disease ICU scoring systems (APACHE II) was measured:
   - Was the effect of ibuprofen on mortality modified by the value of the APACHE score at baseline?
   - Could knowledge of the baseline APACHE score help in medication?
2. How did the effect of ibuprofen on body temperature change over time?

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What is -emc-?

- An easy-to-use prefix command for visualizing
  - the (exponentiated) difference (contrast) between two linear predictions
  - possible effect modifications
- Estimates contrasts for a set of values from the effect modifier.
- Results are saved both as variables and in a matrix

Simple example:

```
emc, at(0(10)40): binreg fate treat apache c.tempc0, rd
```

__apache	__apache_contrast	__apache_lb	__apache_ub
0	-0.391	-0.775	-0.007
10	-0.005	-0.130	0.121
20	-0.057	-0.211	0.097
30	0.062	-0.118	0.242
40	0.221	-0.169	0.611

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-emc- in summary

Syntax: **emc, at(numlist) [options]: regression command**

- required in regression command: outcome(not in stcox) exposure(binary) modifier

Options (some):

- **at**
- **n**knots
- **e**form
- **twoway options**

See Bruun (n.d.)

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Principle behind -emc- by graph

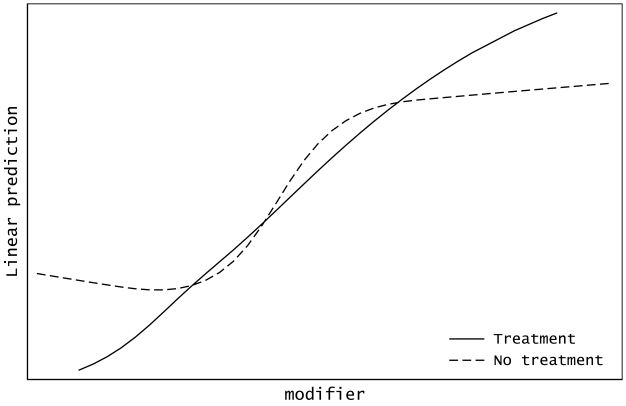

Figure 1: What is the difference in linear prediction between treated and untreated for each value of the modifier?

Principle behind -emc-, summary

1. Model the linear prediction of the outcome dependent on the modifier conditioned on each of the exposure values using eg
   - cubic splines
   - fractional polynomials
2. Estimate exposure contrast points (treated - untreated) with confidence intervals for selected values of the modifier
   - Estimates for the two effects are modelled as independent.
   - Hence, the standard error of the effect is easy to estimate at any value of the modifier

-emc- is based on restricted cubic splines

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Restricted cubic splines by graph

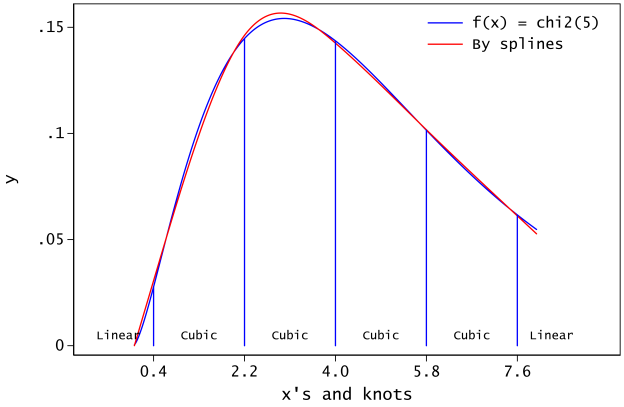

Figure 2: How restricted cubic splines work!

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Restricted cubic splines, summary

1. Cubic splines are piecewise third order polynomials approxmating the curve of two continuous variables
2. Cubic splines are smothed where they meet at the knots
3. Cubic splines are split at a set of values (eg percentiles) on the x-axis (knots)
4. *Restricted* cubic splines are forced to be linear at both ends of the curve

See eg Harrell (2015), Orsini and Greenland (2011) and -mkspline- in StataCorp LLC (2017)

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Getting data

The dataset of 455 sepsis patients are from Dupont (2004) and described in Dupont (2009)

To get

```
use "http://biostat.mc.vanderbilt.edu/dupontwd/wddtext/data/1.4.11.Sepsis.dta", clear
```

Comments:

- Temperature variables are converted to deg. Celsius

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Metadata for the dataset

Name	Index	Label	Value Label Name	Format	Value Label Values	n	unique	missing
id	1	Patient ID		%9.0g		455	455	0
treat	2	Treatment	treatmnt	%9.0g	0 "Placebo" 1 "Ibuprofen"	455	2	0
race	3	Race	race	%9.0g	0 "White" 1 "Black" 2 "Other"	455	3	0
apache	4	Baseline APACHE Score		%9.0g		454	38	1
o2del	5	Oxygen Delivery at Baseline (ml/min/m$\hat{2}$)		%9.0g		168	168	287
fate	6	Mortal Status at 30 Days	fate	%9.0g	0 "Alive" 1 "Dead"	455	2	0
followup	7	Follow-up (hours)		%9.0g		455	148	0
tempc0	8	Temp. (deg. C) at 0 hours		%9.0g		455	122	0
tempc2	9	Temp. (deg. C) at 2 hours		%9.0g		420	106	35
tempc4	10	Temp. (deg. C) at 4 hours		%9.0g		402	108	53
tempc8	11	Temp. (deg. C) at 8 hours		%9.0g		418	113	37
tempc12	12	Temp. (deg. C) at 12 hours		%9.0g		421	111	34
tempc16	13	Temp. (deg. C) at 16 hours		%9.0g		422	113	33
tempc20	14	Temp. (deg. C) at 20 hours		%9.0g		432	108	23
tempc24	15	Temp. (deg. C) at 24 hours		%9.0g		413	105	42
tempc28	16	Temp. (deg. C) at 28 hours		%9.0g		407	105	48
tempc32	17	Temp. (deg. C) at 32 hours		%9.0g		401	102	54
tempc36	18	Temp. (deg. C) at 36 hours		%9.0g		399	101	56
tempc40	19	Temp. (deg. C) at 40 hours		%9.0g		402	98	53
tempc44	20	Temp. (deg. C) at 44 hours		%9.0g		406	97	49
tempc72	21	Temp. (deg. C) at 72 hours		%9.0g		403	104	52
tempc96	22	Temp. (deg. C) at 96 hours		%9.0g		316	87	139
tempc120	23	Temp. (deg. C) at 120 hours		%9.0g		382	93	73

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Research questions operationalised

1. Was the difference in mortality (*fate*) between ibuprofen and placebo (*treatment*) modified by the APACHE at baseline (*apache*)? (The analysis is adjusted for baseline body temperature.)
2. How did the body temperature differ between sepsis patients treated with ibuprofen and treated with placebo over time?

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-emc- command

```
emc, at(0(4)40) caption("Favors Ibuprofen", size(small) position(7) orientation(horizontal) ring(0)) ///
note("Favors placebo", size(small) position(11) ring(0)) yline(0, lcolor(red)) ylabel(-1(0.2)1.4, format(%4.1f)) ///
name(emc_apache, replace) ytitle(Difference in mortality): binreg fate treat apache c.tempc0, rd
```

__apache	__apache_contrast	__apache_lb	__apache_ub
0	-0.391	-0.775	-0.007
4	-0.223	-0.435	-0.011
8	-0.062	-0.177	0.052
12	0.021	-0.109	0.150
16	-0.025	-0.141	0.091
20	-0.057	-0.211	0.097
24	-0.029	-0.178	0.121
28	0.030	-0.126	0.187
32	0.094	-0.120	0.307
36	0.157	-0.140	0.454
40	0.221	-0.169	0.611

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Effect of Ibuprofen on mortality by APACHE score

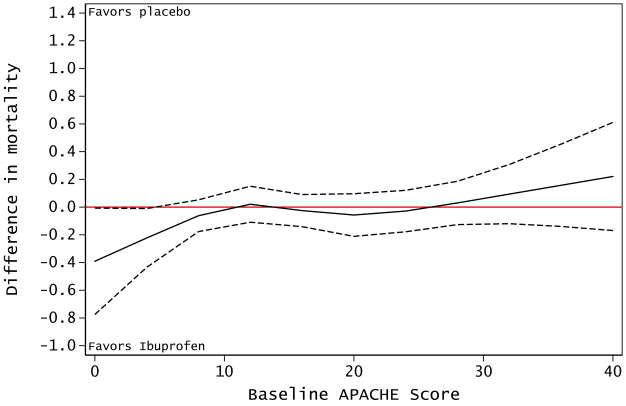

Figure 3: The risk difference of Ibuprofen on mortality. *Does Ibuprofen help when APACHE score is low?*

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Modelling 3rd order polynomial effect modification by the Apache score

See StataCorp LLC (2017) and Mitchell (2012)

```
binreg fate i.treat i.treat##(c.apache c.apache#c.apache c.apache#c.apache#c.apache) c.tempc0, rd
margins, dydx(treat) at(apache=(0(4)40)) noatlegend
marginsplot, ylabel(-1(0.2)1.4, format(%4.1f)) ciopts(fcolor(gs12%40) lcolor(gs12%40) lpattern(solid)) ///
recastci(rarea) recast(line) yline(0, lcolor(red)) name(mgplt3, replace) title("") ///
ytitle(Difference in mortality)
```

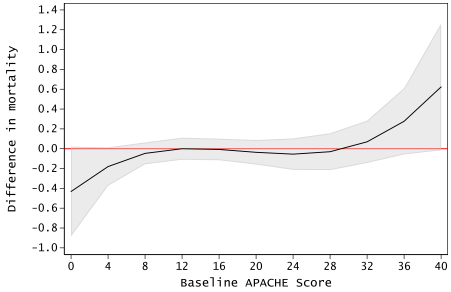

Figure 4: Third order polynomial effect modifications as margins and their 95% confidence intervals.

Modelling linear effect modification by the Apache score

```
binreg fate i.treat i.treat##c.apache c.tempc0, rd
margins, dydx(treat) at(apache=(0(4)40)) noatlegend
marginsplot, ylabel(-1(0.2)1.4, format(%4.1f)) ciopts(fcolor(gs12%40) lcolor(gs12%40) lpattern(solid)) ///
recastci(rarea) recast(line) yline(0, lcolor(red)) name(mgplt3, replace) title("") ///
ytitle(Difference in mortality)
```

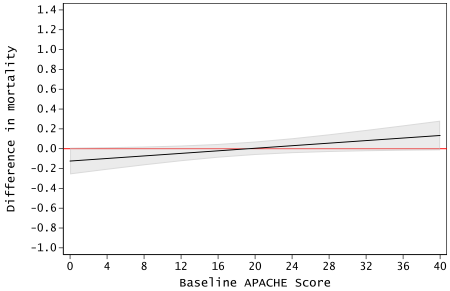

Figure 5: Linear effect modifications as margins and their 95% confidence intervals.

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Preparing data and the -emc- command used

Using -reshape- to make the dataset long on temperature and adding a time variable

```
keep id treat tempc*
reshape long tempc, i(id) j(time)
label variable time "Time from baseline (hours)"
```

Making the graph

```
emc, at(0(5)120) caption("Favors Ibuprofen", size(small) position(7) orientation(horizontal) ring(0)) ///
note("Favors placebo", size(small) position(11) ring(0)) yline(0) ///
ytitle(Temperature difference (deg. C)) legend(on, order(1 "Expected" 2 "95% CI")) ///
xlabel(0(20)120) xline(44) name(emc_tmp, replace) ///
: regress tempc i.treat c.time, vce(cluster id)
```

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Effect of Ibuprofen on body temperature at sepsis patients over time

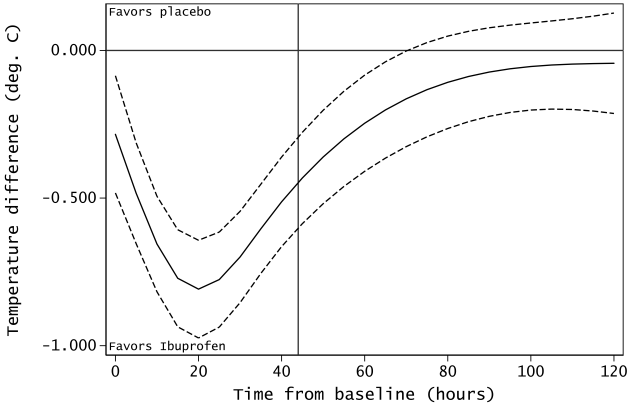

Figure 6: The mean difference on temperture over time between Ibuprofen and placebo at cases of sepsis. Vertical line is the end of 44 hours of ibuprofen therapy. This curve is harder to model using -margins- and -marginsplot-.

Pros and Cons, -emc-

- Pros
  - Easy to use
  - No need to find the underlying function
  - Visualises complex dependencies (linear prediction contrasts dependent on a modifier)
- Cons
  - Underlying function not know
  - Know your link functions
  - More limited in scope than -margins- and -marginsplot-

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Questions? References

Bernard, Gordon R., Arthur P. Wheeler, James A. Russell, Roland Schein, Warren R. Summer, Kenneth P. Steinberg, William J. Fulkerson, et al. 1997. "The Effects of Ibuprofen on the Physiology and Survival of Patients with Sepsis." *New England Journal of Medicine* 336 (13): 912–18. https://doi.org/10.1056/NEJM199703273361303.

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