Nonlinear normative score calculators for NACC UDS3 cognitive tests

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Alzheimer's Disease Centers Program

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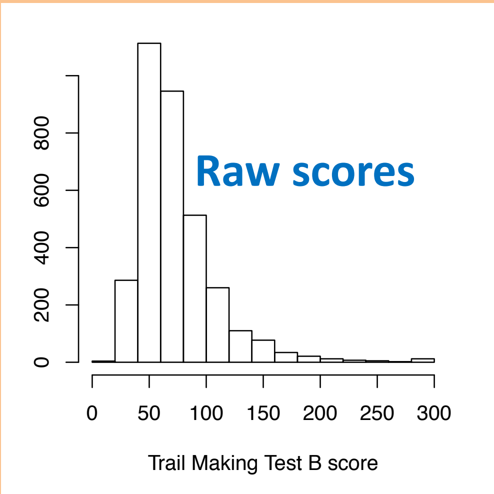
NACC UDS of normal controls – Weintraub et al. (2018)

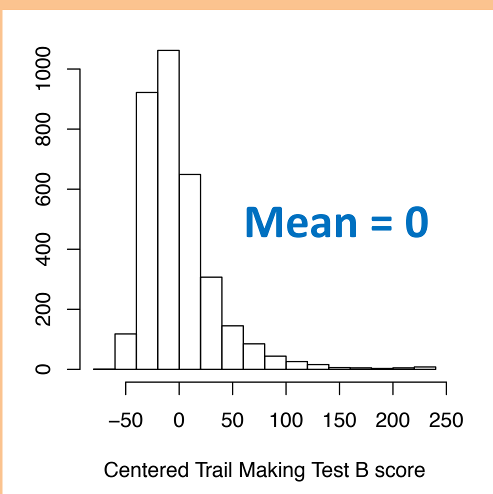
- 3,461 Individuals (Caucasian subset with complete data)
- 29 ADCS
- *Outcomes considered* – **Trail Making Test** A & **B**, Letter fluency F & L &, **Category fluency – animals** & vegetables, Multilingual Naming test total, Number Span longest digit forward & backward, Craft memory – immediate & delay, Benson figure – copy & recall, Montreal Cognitive Assessment (or MoCA), Number Span forward & backward total correct trials
- Assume data approximates distribution of "healthy controls" for each outcome
- ***Objective* – to detect extremely "bad" scores relative to the control distribution – indicative of dementia (focus on FTD)**

Basic "normative" Z-scores

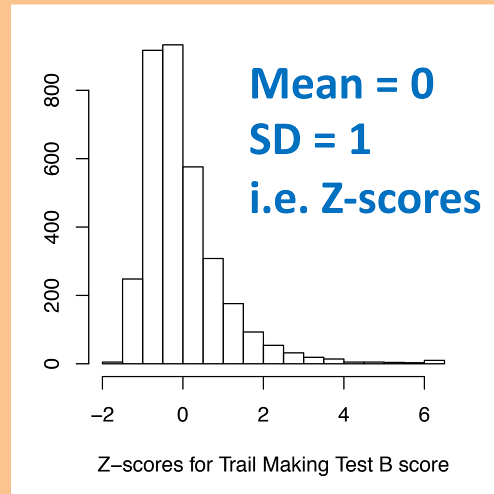


Consider a single neuropsychological test -- e.g. Trail Making Test B (TRAILB)

Subtract mean



Divide by SD

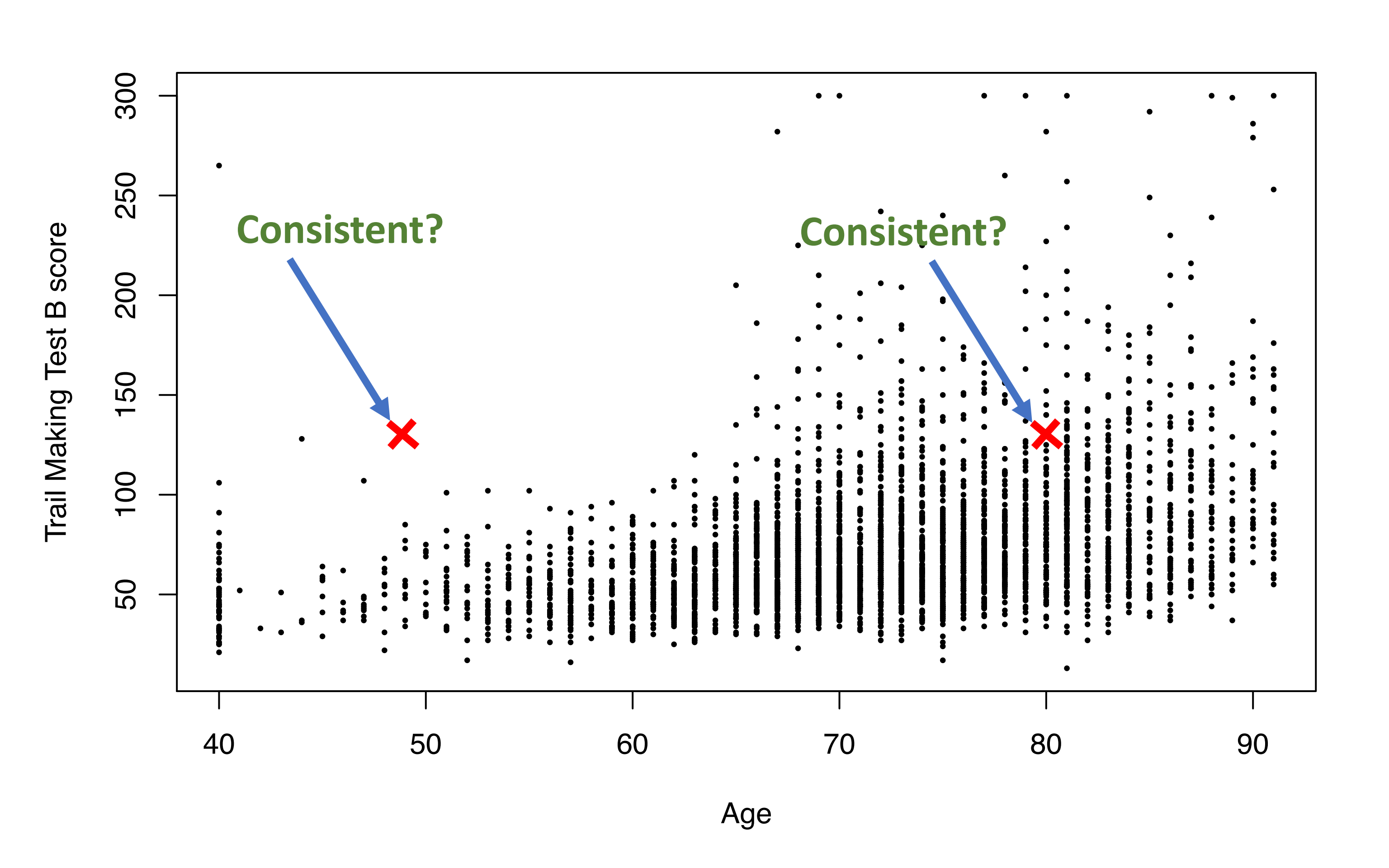


Extreme Z-scores (e.g. > 2 or < -2) indicative of cognitive impairment

For a new individual: take score, subtract mean, divide total by SD, and compare with Z-score distribution

Allows uniform comparison across scores

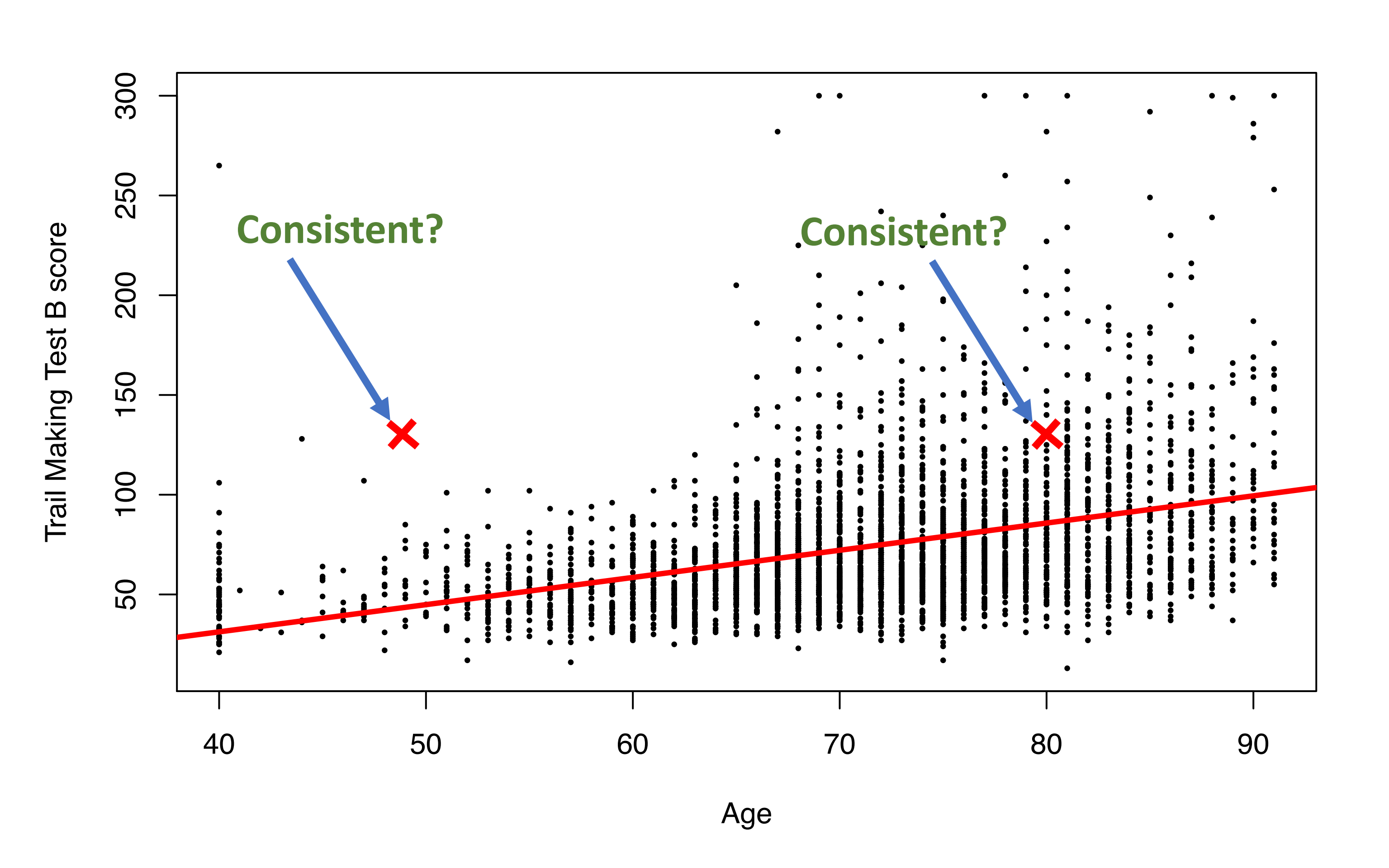
But… "normal scores" for younger people not same as for older



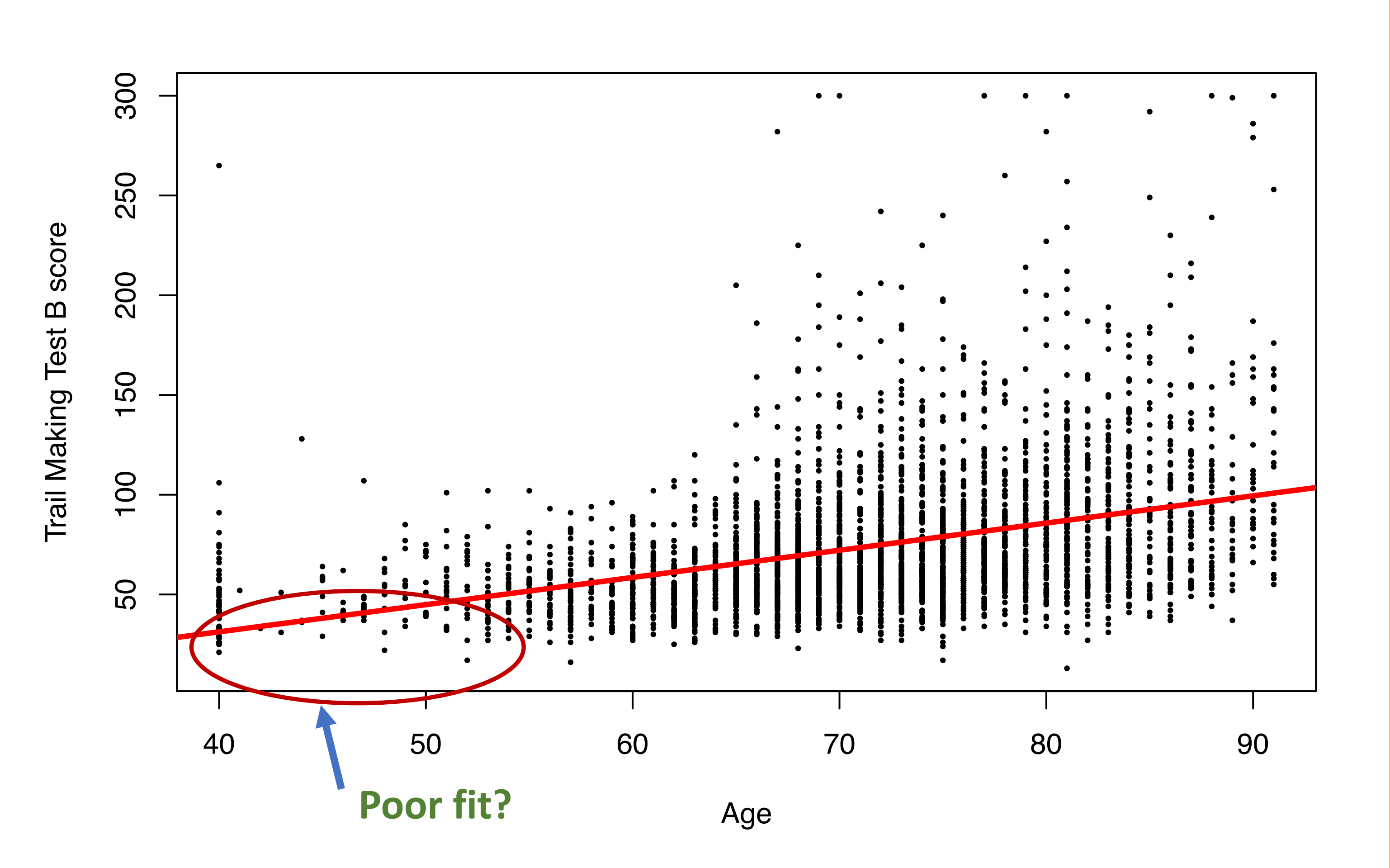
Linearly corrected Z-scores

- Linear approach: fit a linear regression to “adjust for” age, sex and education level -- Weintraub et al. (2018)
- To score a new individual – 2-stage process:
    1. Adjust test score with fitted regression -- i.e. subtract predicted value for the individuals age, sex and education
    2. Turn the adjusted test score into a z-score by dividing by linear regression residual standard deviation estimate

Linear regression for age

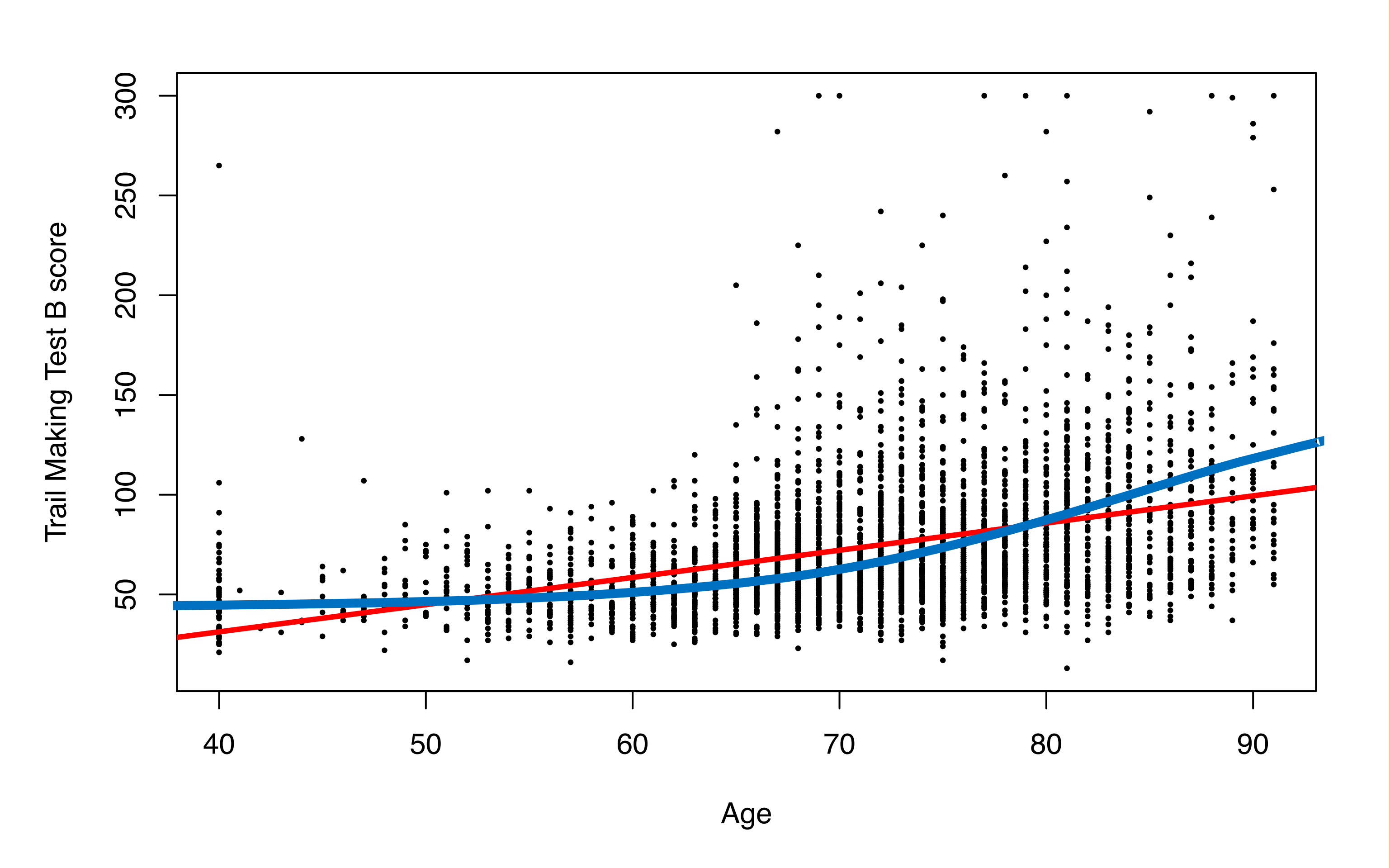


Linear regression for age – issue 1

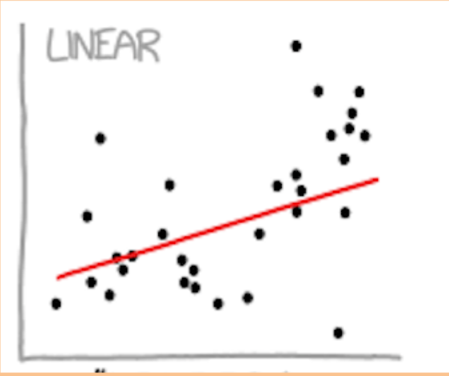


FTD often occurs in this lower age range

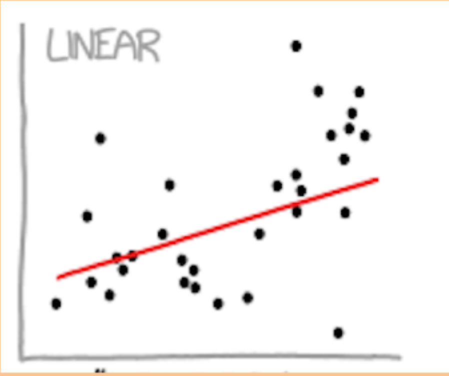
Issue 1: Can we improve on the straight line fit with a nonlinear fit?



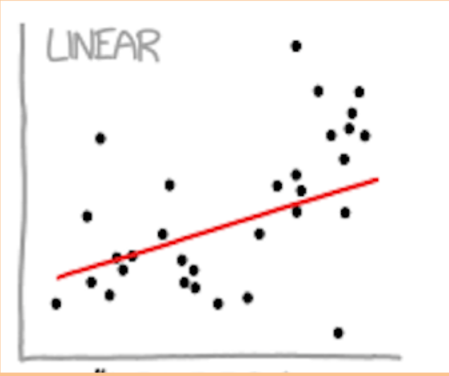
But, is nonlinear regression the right thing to do?



Is nonlinear regression the right thing to do?



Is nonlinear regression the right thing to do?

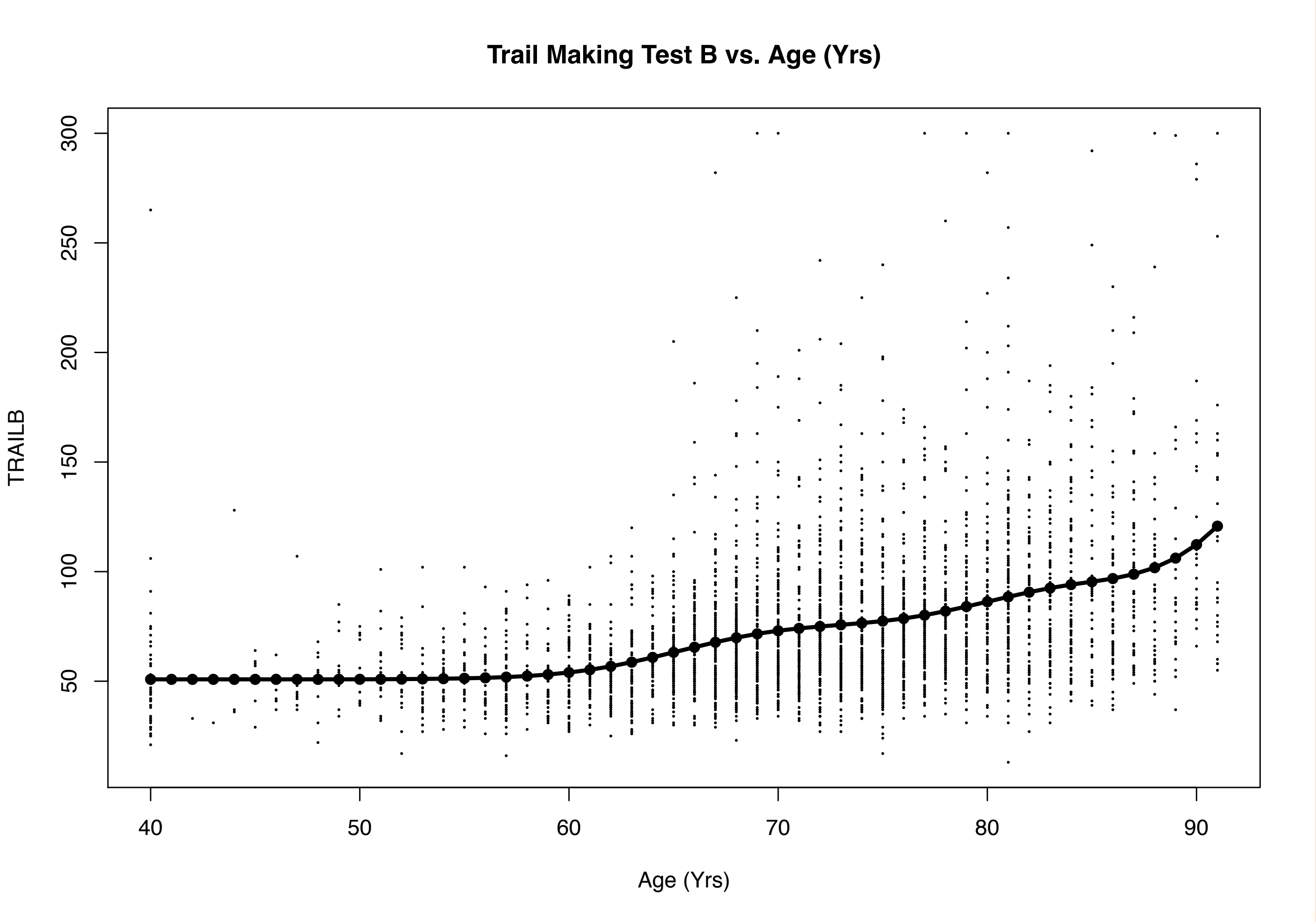


We do need to be careful when fitting nonlinear models that we do not "overfit"

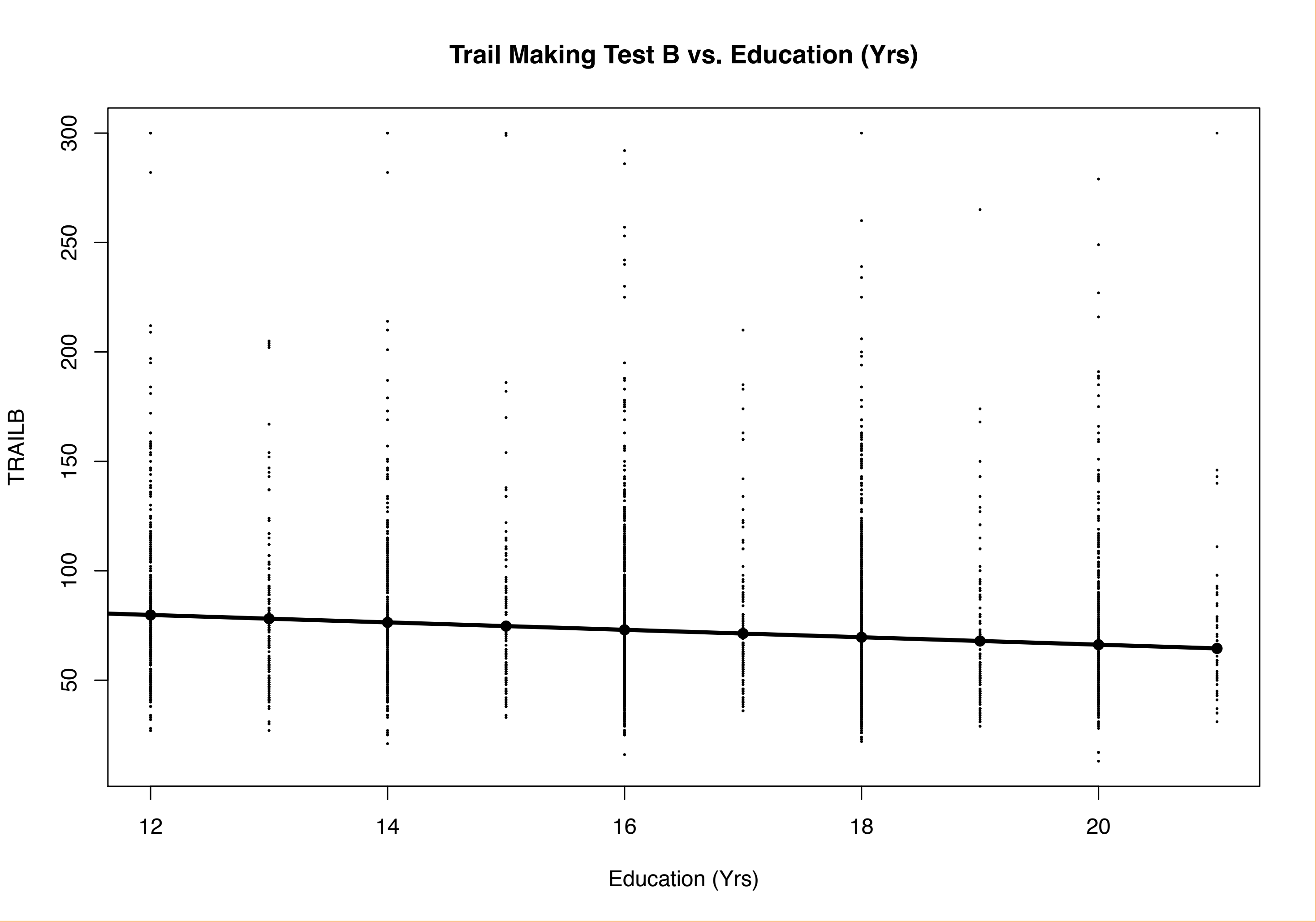
Present solution: use shape constrained additive models (SCAMs)

- Generalized additive models (GAMs) – flexible "smooth" curves to fit data – Hastie & Tibshirani (1986)
- Extend to shape constrained models (SCAMs) -- strictly increasing or decreasing fits – Pya & Wood (2015)
- GAMs/SCAMs use a set of smooth "basis functions" (e.g. P-splines = penalized B-splines) – knitted together with "nice" mathematical properties form a smooth function
- Avoids overfitting by *cross-validating* – **checks for a "genuinely improved fit" when adding complexity**
- We use SCAM to regress on Age, Sex and Education

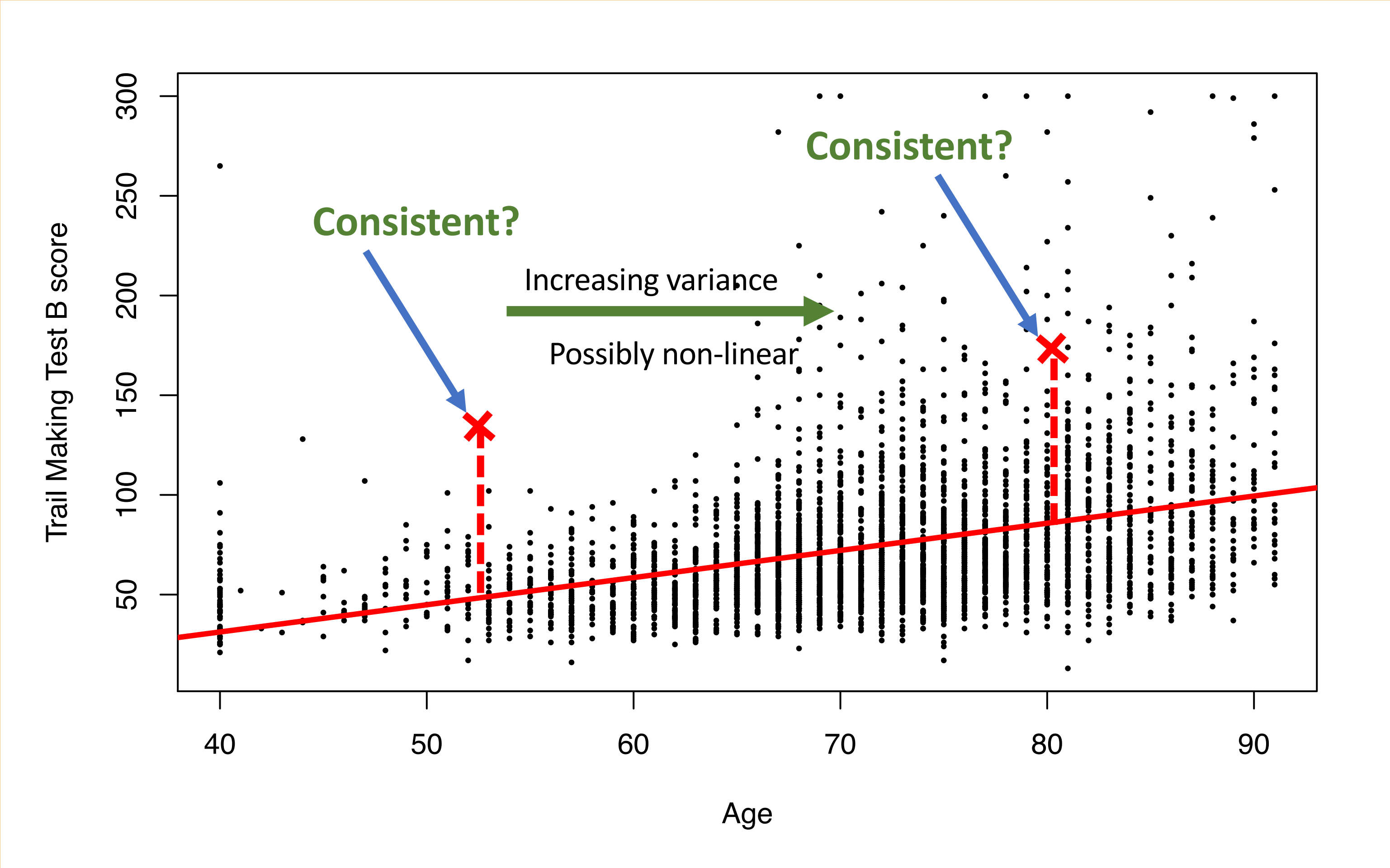
SCAM fitted model: TRAILB vs Age



SCAM fitted model: TRAILB vs ED.

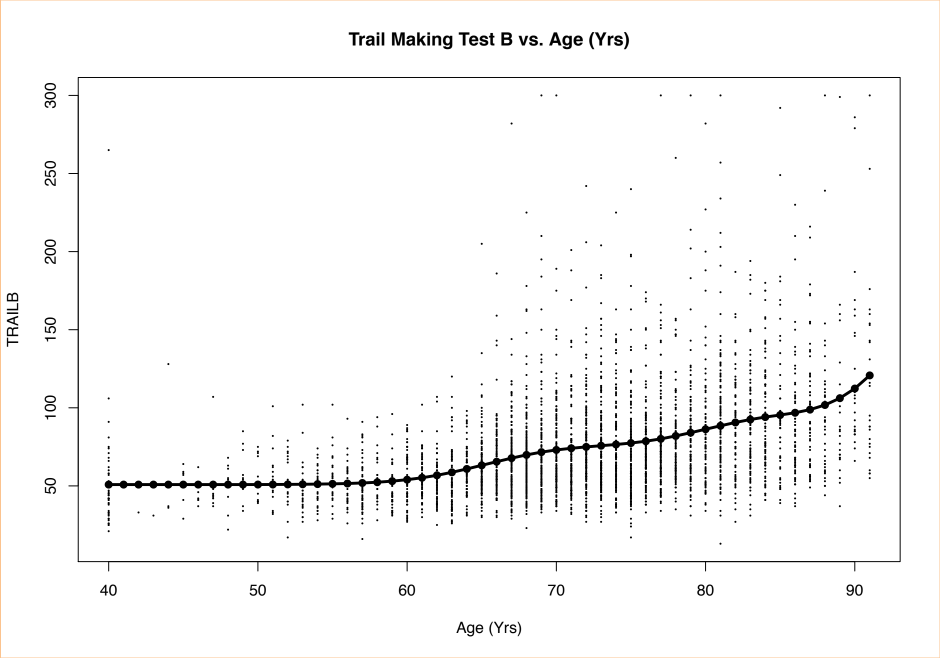


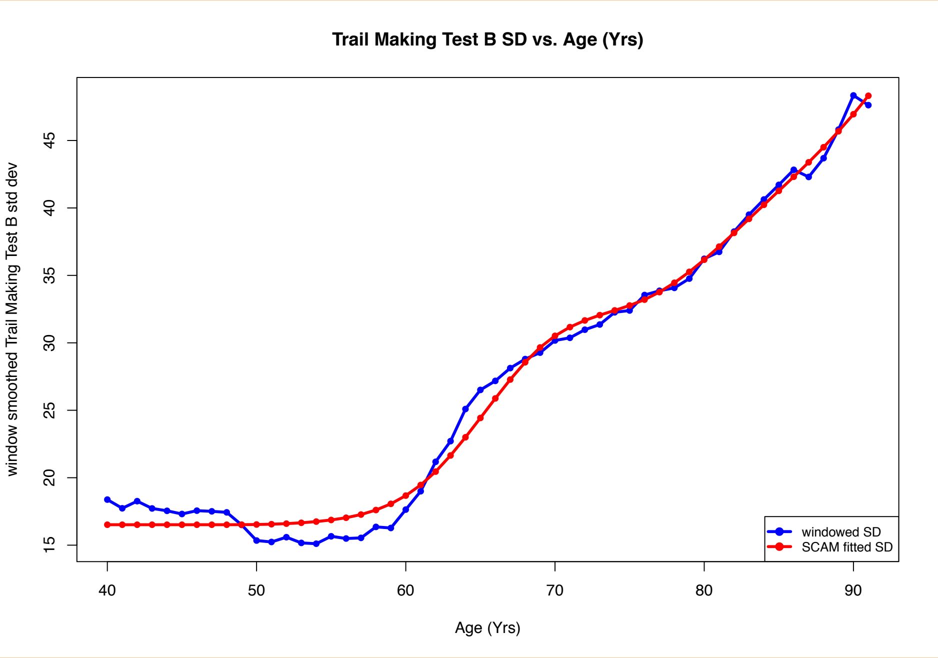
Linear regression for age – issue 2



Issue 2: Account for increasing variance - SCAM fitted model: SD vs Age

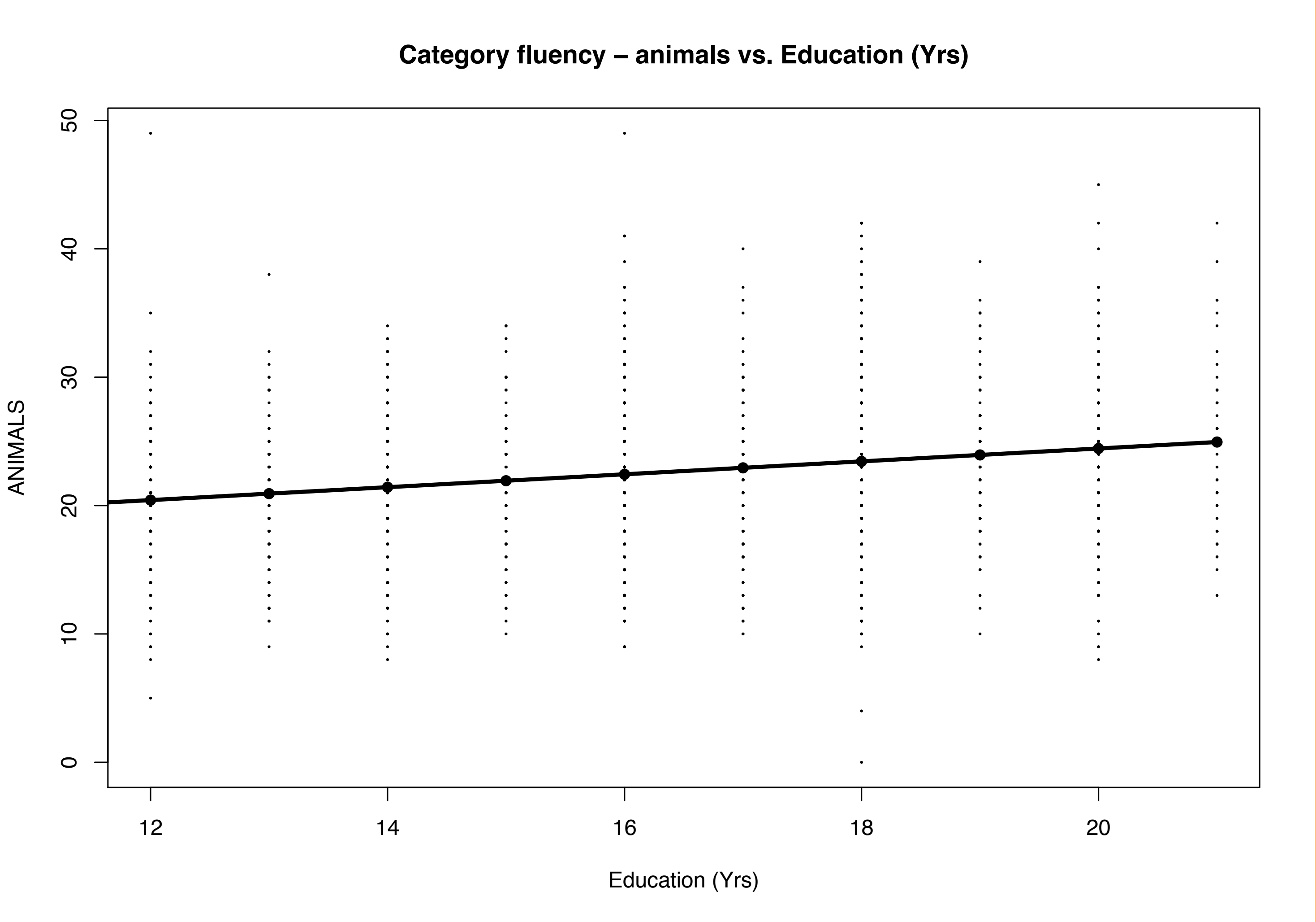
Estimate standard deviation with age based on an 11 year window (blue line) and fit SCAM



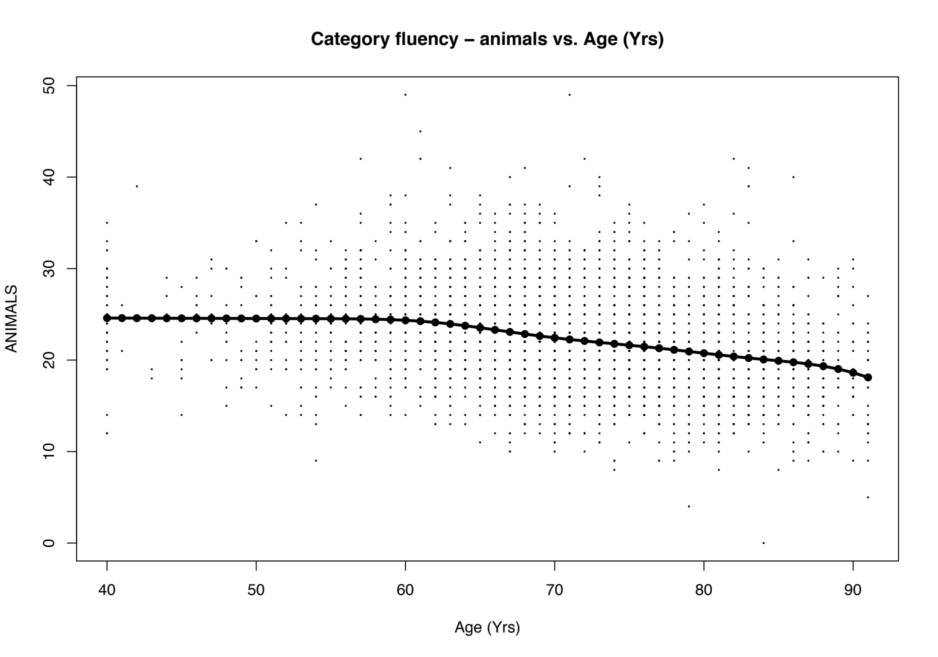


SCAM fitted model: ANIMALS vs Age

SCAM fitted model: ANIMALS vs ED.



SCAM fitted model: ANIMALS SD vs Age



Procedure – look up table for TRAILB

	A	B	C	D	E
1	NACCAGE	EDUC	SEX	mean.adj	sd.adj
2	40	11	0	119.487918	7.55301009
3	41	11	0	119.500457	8.22482161
4	42	11	0	119.513383	8.89728201
5	43	11	0	119.526919	9.5707555
6	44	11	0	119.54129	10.2456063
7	45	11	0	119.556723	10.9221986
8	46	11	0	119.57344	11.6008966
9	47	11	0	119.591668	12.2820646
10	48	11	0	119.611631	12.9660668
11	49	11	0	119.634357	13.6532756
12	50	11	0	119.674358	14.3442042
13	51	11	0	119.757334	15.0394822
14	52	11	0	119.909324	15.7397425
15	53	11	0	120.156368	16.4456183
16	54	11	0	120.524504	17.1577428
17	55	11	0	121.039773	17.8767489
18	56	11	0	121.728213	18.6032698
19	57	11	0	122.615833	19.3379382
20	58	11	0	123.713499	20.0812027
21	59	11	0	124.992335	20.833029
22	60	11	0	126.417026	21.5933045
23	61	11	0	127.95226	22.3619164

For a new patient:

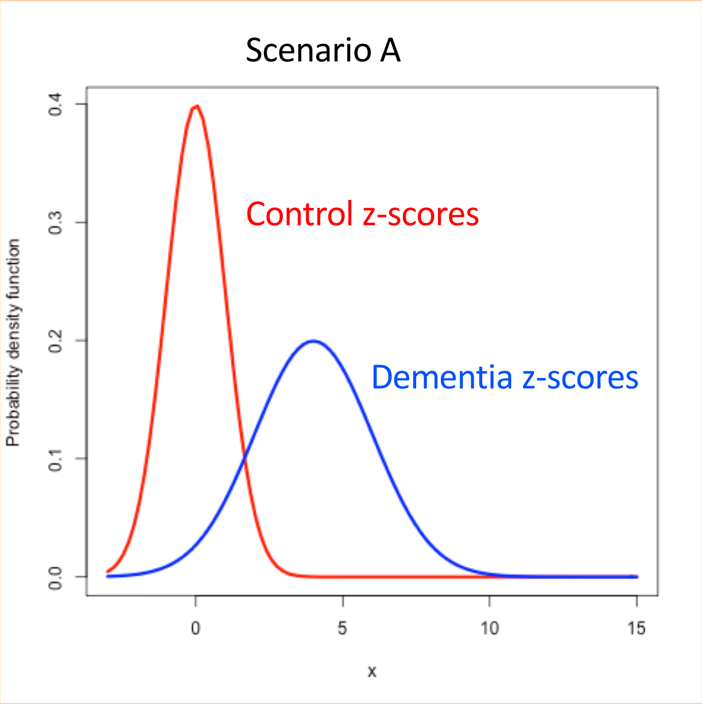
1. Obtain the patient’s TRAILB score
2. Find the row in the table corresponding to the patients, age, education level and sex (0=M, 1=F) – extract value for mean.adj and sd.adj
3. Take the patient’s TRAILB score, subtract mean.adj, then divide by sd.adj = patient’s z-score

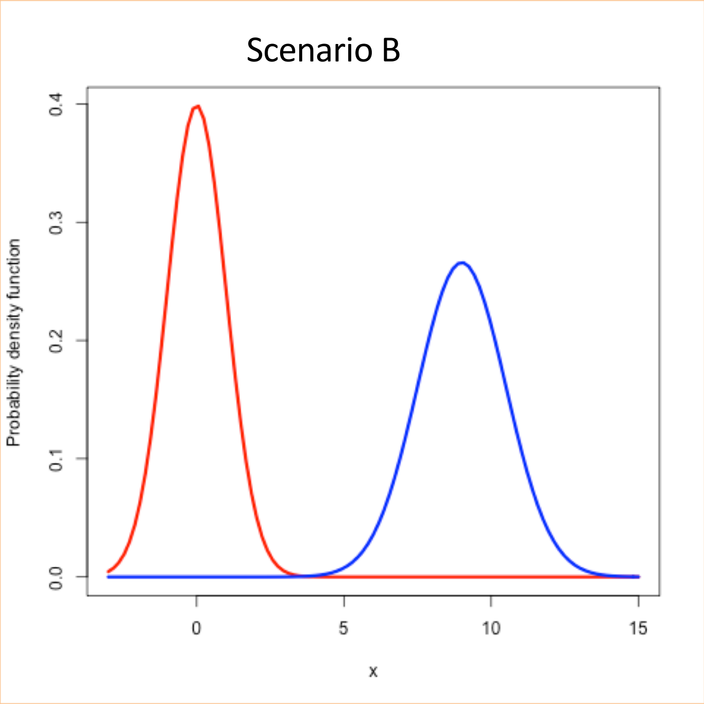
$$z = \frac{x - \mu}{\sigma} = \frac{x - \mathrm{mean.adj}}{\mathrm{sd.adj}}$$

Limitations

- Nonlinear models need more “manipulation” to fit
- Ad hoc SD windowing technique
- Non-normally distributed variation in some variables
- Caucasians only
- Based only on normative individuals

Never lose sight that ideal solution needs distribution of dementia group Z-scores





Optimal Z-score cut-point for classifying dementia depends on the distribution of the dementia Z-scores

Conclusions

- Nonlinear model fitting via SCAMs provides greater improvement in fit (over linear) for the relationship between the predictors (age, sex and education level) and neurocognitive outcomes in the control population.
- Nonlinear modeling thereby leads to adjusted Z-scores that are more representative of the departures from cognitively normal levels relative to their specific age, sex, and education level.

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