

Historical controls: think cluster not parallel

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Acknowledgements

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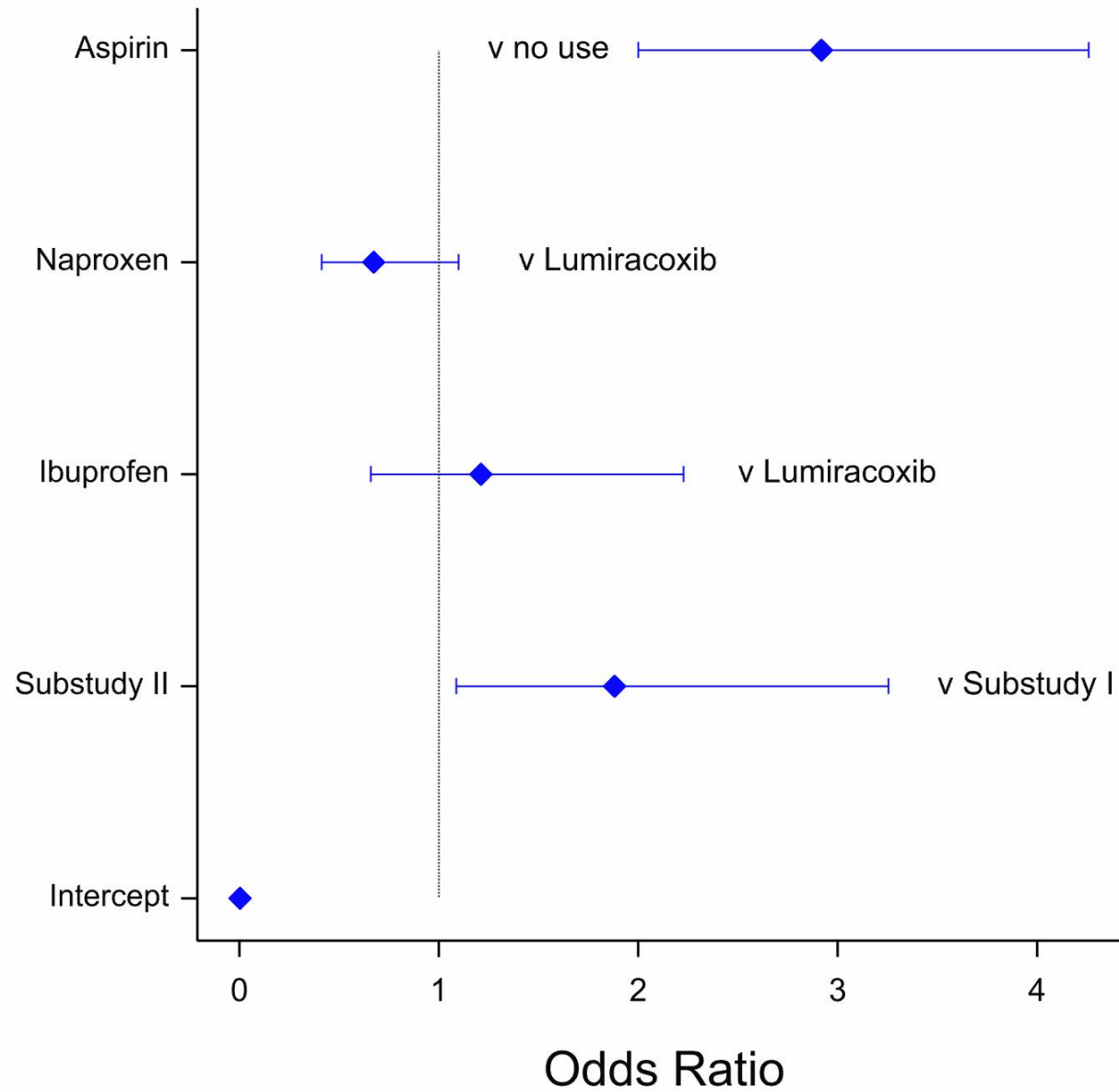
TARGET study

- Trial of more than 18,000 patients in osteoarthritis over one year or more
- Two sub-studies
 - Lumiracoxib v ibuprofen
 - Lumiracoxib v naproxen
- Stratified by aspirin use or not
- Has some features of a randomised trial but also some of a non-randomised study

	Sub-Study 1		Sub Study 2	
Demographic Characteristic	Lumiracoxib n = 4376	Ibuprofen n = 4397	Lumiracoxib n = 4741	Naproxen n = 4730
Use of low-dose aspirin	975 (22.3)	966 (22.0)	1195 (25.1)	1193 (25.2)
History of vascular disease	393 (9.0)	340 (7.7)	588 (12.4)	559 (11.8)
Cerebro-vascular disease	69 (1.6)	65 (1.5)	108 (2.3)	107 (2.3)
Dyslipidaemias	1030 (23.5)	1025 (23.3)	799 (16.9)	809 (17.1)
Nitrate use	105 (2.4)	79 (1.8)	181 (3.8)	165 (3.5)

	Model Term		
Demographic Characteristic	Sub-study (DF=1)	Treatment given Sub-study (DF=2)	Treatment (DF=2)
Use of low-dose aspirin	< 0.0001	0.94	0.0012
History of vascular disease	< 0.0001	0.07	<0.0001
Cerebro-vascular disease	0.0002	0.93	0.0208
Dyslipidaemias	<0.0001	0.92	<0.0001
Nitrate use	< 0.0001	0.10	<0.0001

TARGET odds ratios CV event



Lumiracoxib v Lumiracoxib

	Statistic	
Outcome Variables	Deviance	P-Value
Total of discontinuations	13.61	0.0002
CV events	2.92	0.09
At least one AE	1.73	0.19
Any GI	21.31	<0.0001
Dyspepsia	47.34	< 0.0001

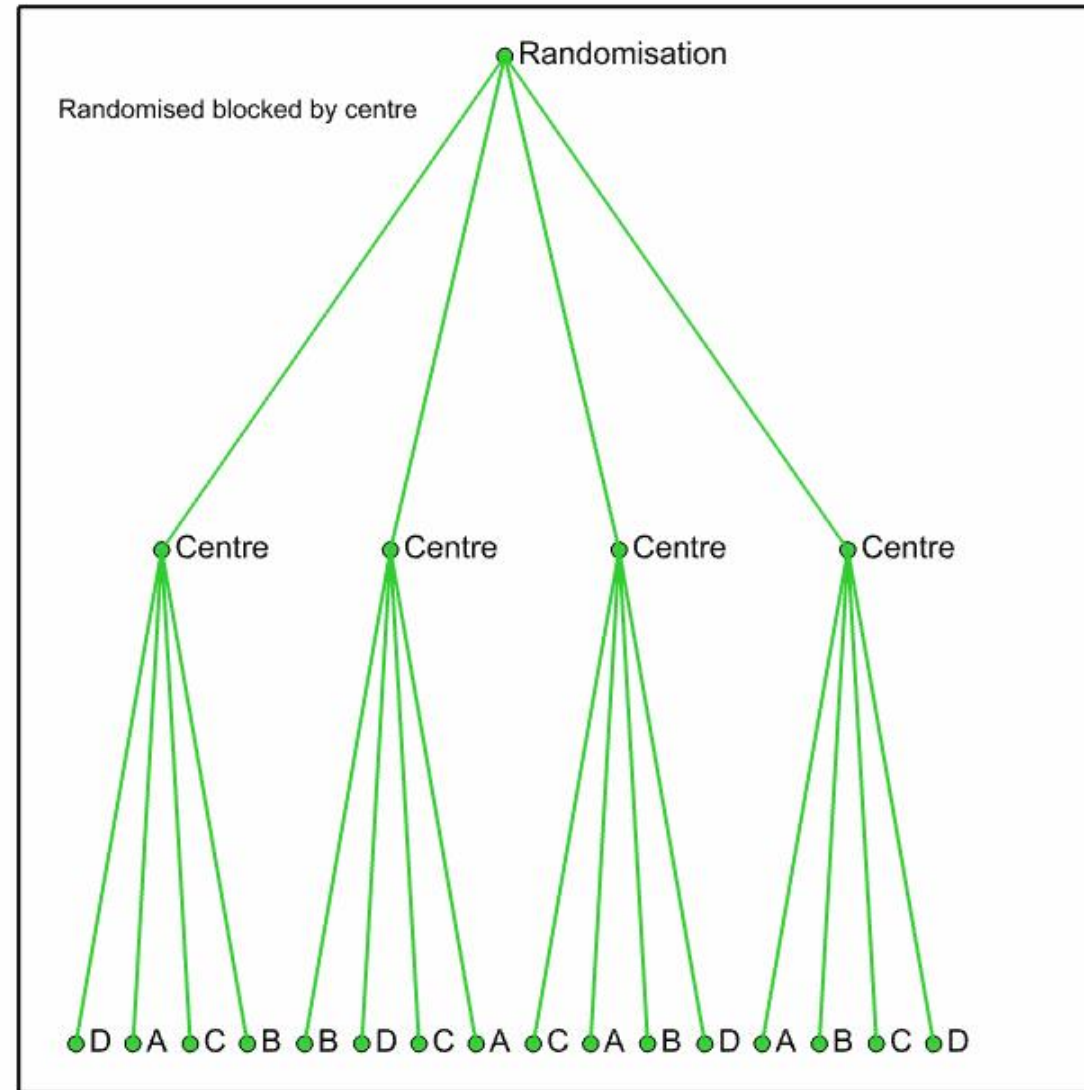
A big data analyst is an expert at reaching misleading conclusions with huge data sets, whereas a statistician can do the same with small ones

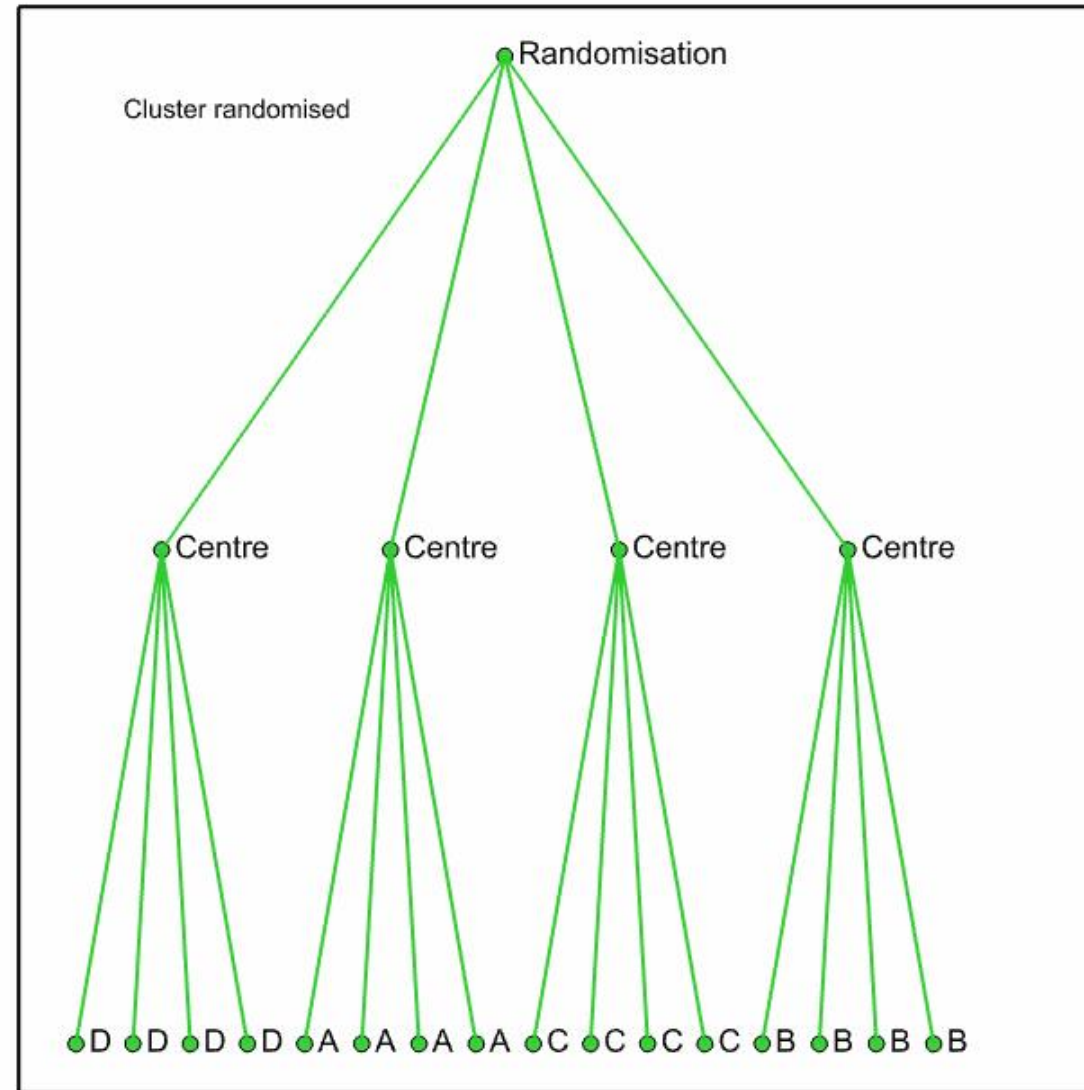
Data Filtering Some Examples

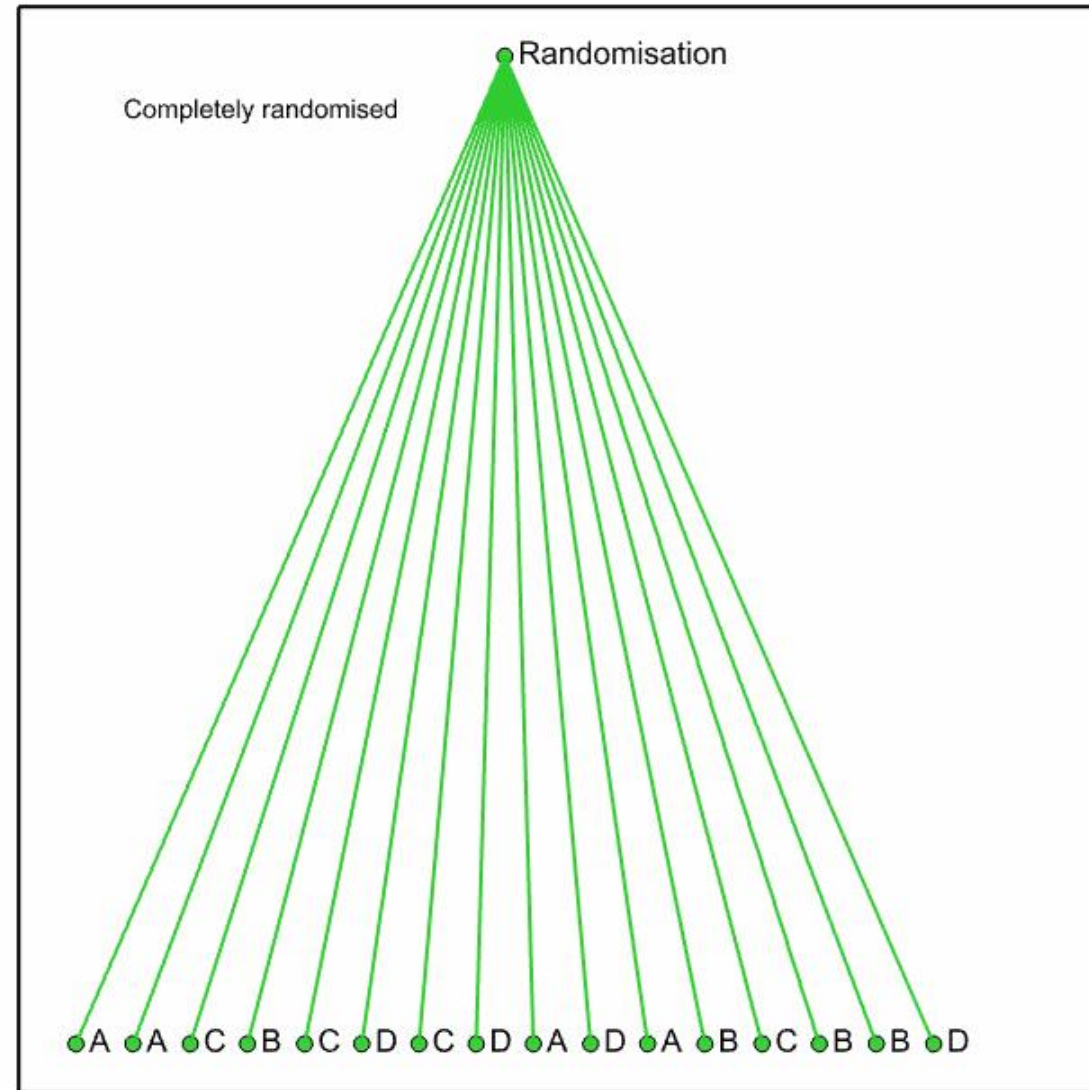
- Oscar winners lived longer than actors who didn't win an Oscar
- A 20 year follow-up study of women in an English village found higher survival amongst smokers than non-smokers
- Transplant receivers on highest doses of cyclosporine had higher probability of graft rejection than on lower doses
- Left-handers observed to die younger on average than right-handers
- Obese infarct survivors have better prognosis than non-obese

Moral

- What you don't see can be important
- For some purposes just piling on data does not really help
- What helps are
 - Careful design
 - Thinking!
- The TARGET study provides non-randomised control data that will be as good as (in practice much better) than any historical data you will find
 - These data are still not good enough







Moral

- We have a tendency to think that historical controls are slightly inferior concurrent controls
- Has led some to just propose a naïve discounting
- However such controls were not treated under similar conditions in the same centres
- They were treated in different centres
- At the very least we have the variability of a cluster-randomised trials
- In practice things will be worse

Implications for using historical controls

- Identification, pre-specification and agreement on a suitable historical data-set
 - Because otherwise you could pick and choose your historical controls
- An agreed, enforceable and checkable plan for recruiting the experimental arm in advance of doing so
 - Because otherwise you could selectively recruit to your advantage
- A finalised analysis plan prior to beginning the trial
 - Because blinding is impossible
- Use of a hierarchical model with sufficient complexity
 - Because many components of variation are involved
- Emphasis on number of historical trials rather than patients
 - Because otherwise components of variation cannot be estimated

We tend to believe “the truth is in there”, but sometimes it isn’t and the danger is we will find it anyway

Suggested reading

Schmidli, H., Gsteiger, S., Roychoudhury, S., O'Hagan, A., Spiegelhalter, D. and Neuenschwander, B., 2014. Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, 70(4), pp.1023-1032.

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Senn, S., Gavini, F., Magrez, D. and Scheen, A., 2013. Issues in performing a network meta-analysis. *Statistical Methods in Medical Research*, 22(2), pp.169-189.

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