

Statistical Modeling of Carryover Effects After Cessation of Treatments

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TROPHY



TRial Of Preventing HYpertension

- ▶ 809 participants with systolic blood pressure (BP) 130 - 139 mm Hg randomised
- ▶ 69% of those diagnosed with hypertension did so by having 3 measurements above 140 mm Hg
- ▶ Treatment 53.2%, Placebo 63.0% cumulative diagnosis

TROPHY

They concluded that “...the effect of active treatment on delaying the onset of hypertension can extend up to 2 years after the discontinuation of treatment. “

Criticism

Meltzer (2006)

- ▶ “idiosyncratic primary endpoint seriously impairs external applicability”

Persell and Baker (2006)

- ▶ Cumulative diagnosis rates would differ even with identical underlying BP

Lumley, Rice and Psaty (2008)

- ▶ Simulations conducted to replicate TROPHY outcomes
- ▶ Without carryover, similar cumulative incidences of hypertension were found in 80% of studies

Trial Design Fails

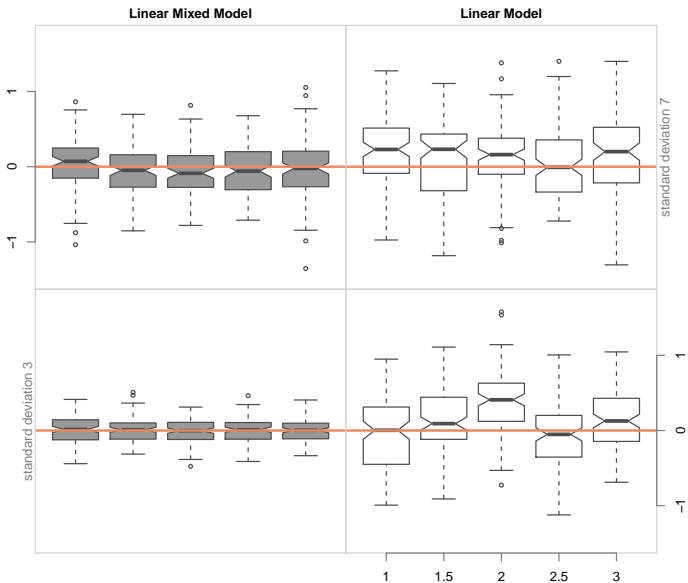
Our simulations have concluded that both a *parallel* and *crossover* designs *fail* when comparing cumulative incidence.

Missing At Random - linear mixed model

Justification:

- ▶ Diagnosis results in treatment in a way that we understand
- ▶ Our data is *missing at random*: probability of dropout depends on past observed values
- ▶ We can find unbiased estimates of carryover parameters

Bias in Estimates



Conclusion

This enables us to estimate the duration of effects of short lifestyle interventions.

For further reading



S. D. Persell and D. W. Baker.

Studying interventions to prevent the progression from prehypertension to hypertension: Does TROPHY win the prize?

American Journal of Hypertension, 19(11):1095–7, 2006.



J. I. Meltzer.

A specialist in clinical hypertension critiques the TROPHY trial.

American Journal of Hypertension, 19(11), 2006.

More reading



T. Lumley, K. M. Rice, and B. M. Psaty.

Carryover effects after cessation of drug treatment: Trophies or dreams?

American Journal of Hypertension, 21:14–16, 2008.



S. Julius, S. D. Nesbitt, B. M. Egan, M. A. Weber, E. L. Michelson, N. Kaciroti, H. R. Black, R. H. Grimm, F. H. Messerli, and S. Oparil.

Feasibility of treating prehypertension with an angiotensin-receptor blocker.

New England Journal of Medicine, 354(16):1685–97, 2006.