The cluster randomized crossover trial: the effects of attrition in the AB/BA design and how to account for it in sample size calculations.

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Previous research

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The Design of Cluster Randomized Crossover Trials

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The inefficiency induced by between-cluster variation in cluster randomized (CR) trials can be reduced by implementing a crossover (CO) design. In a simple CO trial, each subject receives each treatment in random order. A powerful characteristic of this design is that each subject serves as its own control. In a CR CO trial, clusters of subjects are randomly allocated to a sequence of interventions. Under this design, each subject is either included in only one of the treatment periods (CO at cluster level) or in both periods (CO at subject level). In this study, the efficiency of both CR CO trials relative to the CR trial without CO is demonstrated. Furthermore, the optimal allocation of clusters and subjects given a fixed budget or desired power level is discussed.

Keywords: *cluster randomized crossover design; statistical efficiency; optimal allocation*

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Cluster randomized crossover trial

Clusters 1,…, ½k	Treatment A	Treatment B
Clusters ½k+1,…, k	Treatment B	Treatment A

Two different types of design

- Cross-sectional: different subjects in both time periods
- Cohort: same subjects in both time periods

Attrition

- Cluster randomized crossover design is a longitudinal design
- Attrition is the rule rather than the exception
  - rates of 5-10% are not uncommon and can be as high as 25%

- Study on New Nordic diet
  - Pupils in schools; 3.4% attrition of pupils
  - Did not like school meals, changed school or class, disliked the measurements or found them too time-consuming, were lost to follow-up, other reasons
- Study on exercise program for nursing staff
  - Nurses in nursing homes; 7% attrition of nurses (only in sequence program, control)
  - Not being interested in control, pregnancy, sick leave, starting to study or new job

Aim of the study

- Explore the effects of attrition
- Evaluate ways to account for attrition
- Assumptions
  - attrition only occurs during wash-out period
  - attrition rates may vary across treatment sequences
  - missing (completely) at random

Cross-sectional design

- $y_{hij} = \gamma_0 + \gamma_1 x_{1hj} + \gamma_2 x_{2hj} + u_{hj} + e_{ij}$
- (co-)variance components
  - $var(e_{ij}) = \sigma_I^2$
  - $var(u_{1j}) = var(u_{2j}) = \sigma_{CP}^2 + \sigma_C^2$
  - $cov(u_{1j}, u_{2j}) = \sigma_{CP}^2$
- Correlation coefficients
  - $corr(y_{1ij}, y_{1i'j}) = corr(y_{2ij}, y_{2i'j}) = \frac{\sigma_{CP}^2+\sigma_C^2}{\sigma_I^2+\sigma_{CP}^2+\sigma_C^2} = \rho$ w-cluster w-period
  - $corr(y_{1ij}, y_{2i'j}) = \frac{\sigma_{CP}^2}{\sigma_I^2+\sigma_{CP}^2+\sigma_C^2} = \eta.$ w-cluster b-period

Cohort design

- $y_{hij} = \gamma_0 + \gamma_1 x_{1hj} + \gamma_2 x_{2hj} + u_{hj} + e_{ij} + m_{hij}.$
- (co-)variance components
  - $var(m_{hij}) = \tilde{\sigma}_M^2$
  - $var(e_{ij}) = \tilde{\sigma}_I^2$
  - $var(u_{1j}) = var(u_{2j}) = \tilde{\sigma}_{CP}^2 + \tilde{\sigma}_C^2$
  - $cov(u_{1j}, u_{2j}) = \tilde{\sigma}_{CP}^2$
- Correlation coefficients
  - $corr(y_{1ij}, y_{1i'j}) = corr(y_{2ij}, y_{2i'j}) = \frac{\tilde{\sigma}_C^2+\tilde{\sigma}_{CP}^2}{\tilde{\sigma}_C^2+\tilde{\sigma}_{CP}^2+\tilde{\sigma}_I^2+\tilde{\sigma}_M^2} = \rho$ w-cluster w-period
  - $corr(y_{1ij}, y_{2i'j}) = \frac{\tilde{\sigma}_C^2}{\tilde{\sigma}_C^2+\tilde{\sigma}_{CP}^2+\tilde{\sigma}_I^2+\tilde{\sigma}_M^2} = \eta$ w-cluster b-period
  - $corr(y_{1ij}, y_{2ij}) = \frac{\tilde{\sigma}_C^2+\tilde{\sigma}_I^2}{\tilde{\sigma}_C^2+\tilde{\sigma}_{CP}^2+\tilde{\sigma}_I^2+\tilde{\sigma}_M^2} = \xi$ w-cluster w-subject

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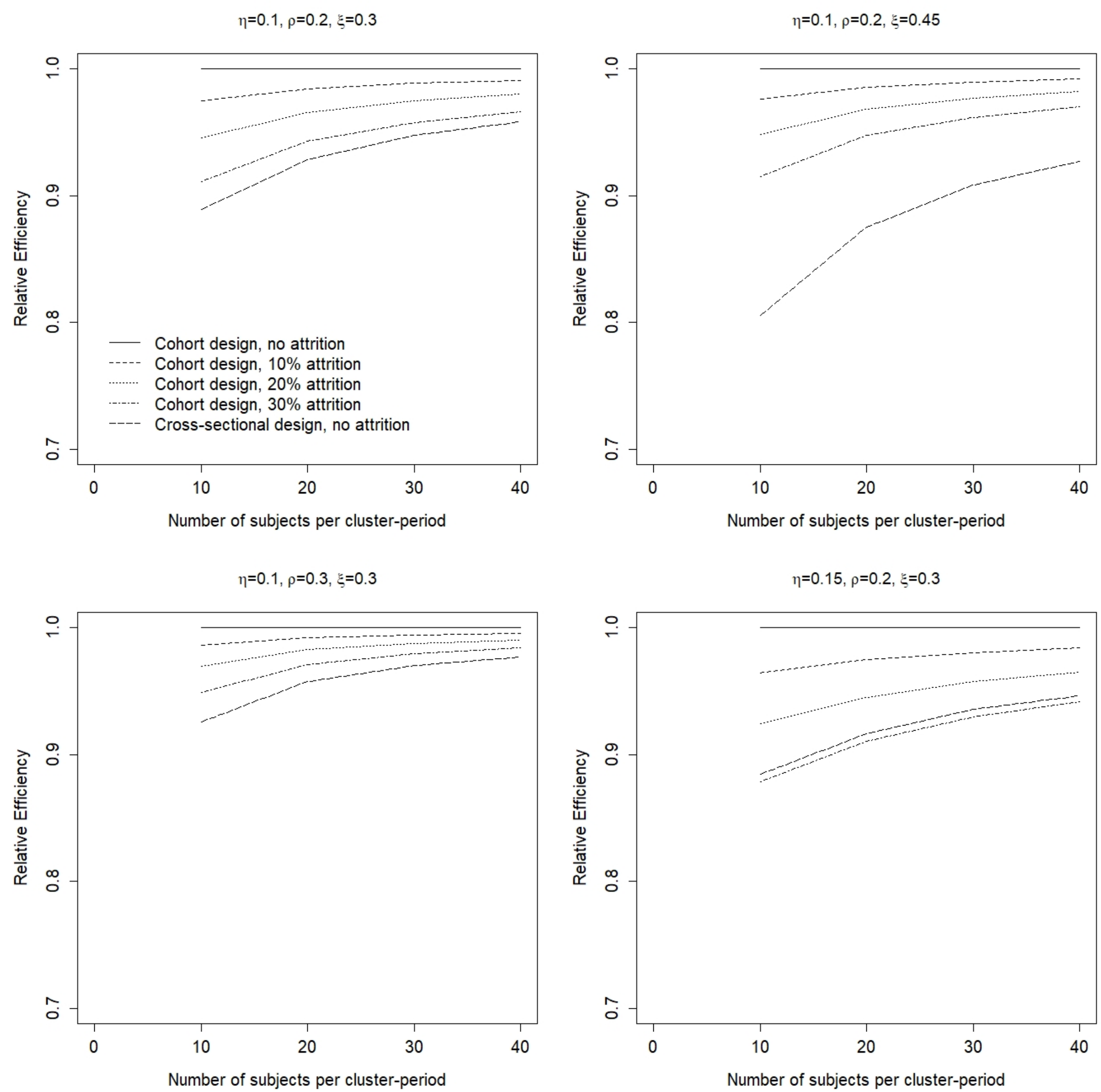
Subject attrition in a cohort design



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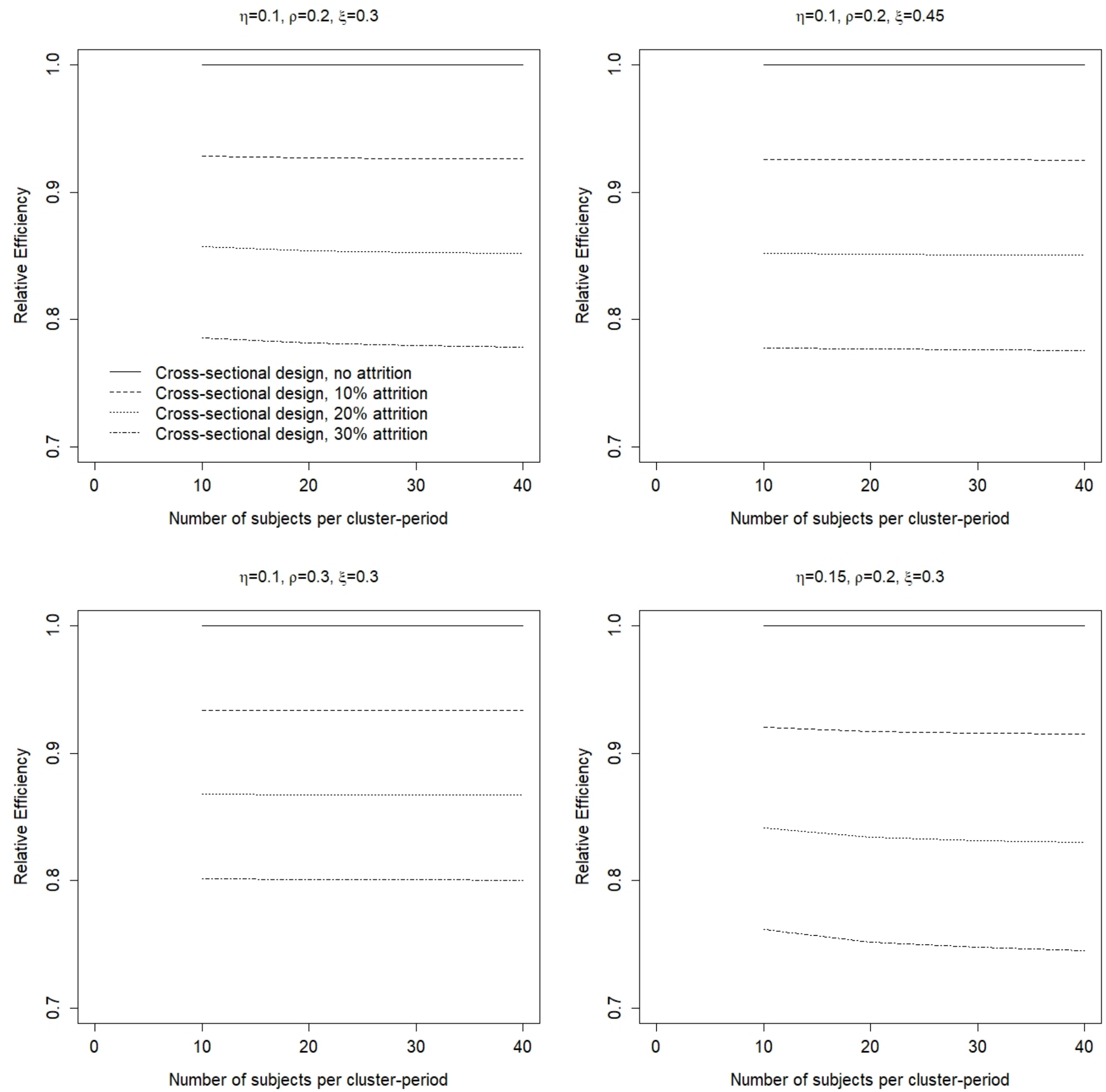
Cluster attrition in a cohort design

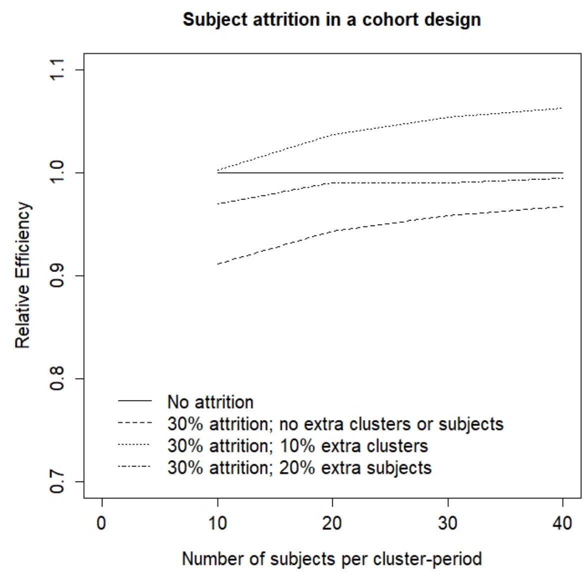


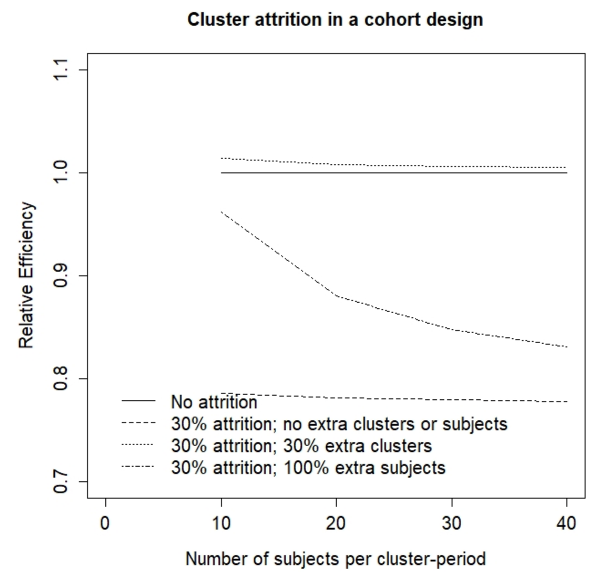
Accounting for attrition

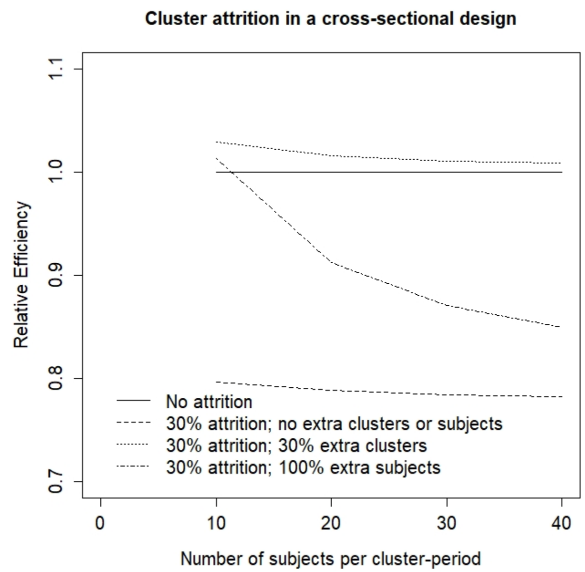
- Anticipated attrition: attrition that a researcher anticipates before the start of the trial.
  - The most obvious strategy to repair for such attrition is increasing the number of subjects and/or clusters from the start of the study onwards.

- Unanticipated attrition: attrition that a researcher does not anticipate before the start of the trial.
  - Only during the washout period does it become clear some subjects or clusters will not continue to the second time period.
  - The most obvious strategy to repair for the loss of efficiency is increasing the number of subjects in the second time period (i.e. no extra clusters sampled).

Accounting for anticipated attrition



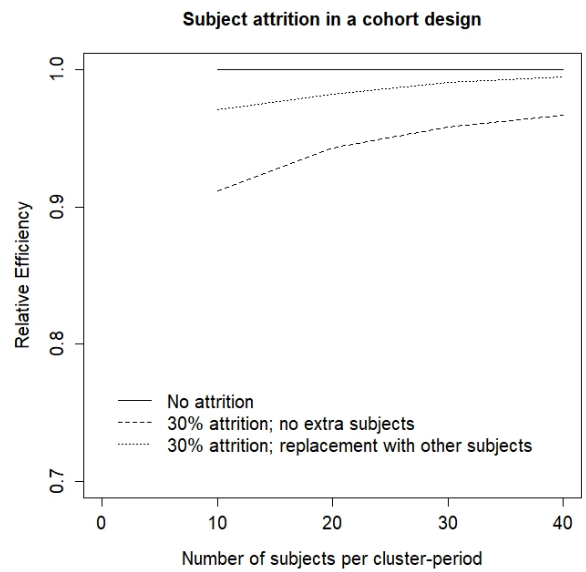


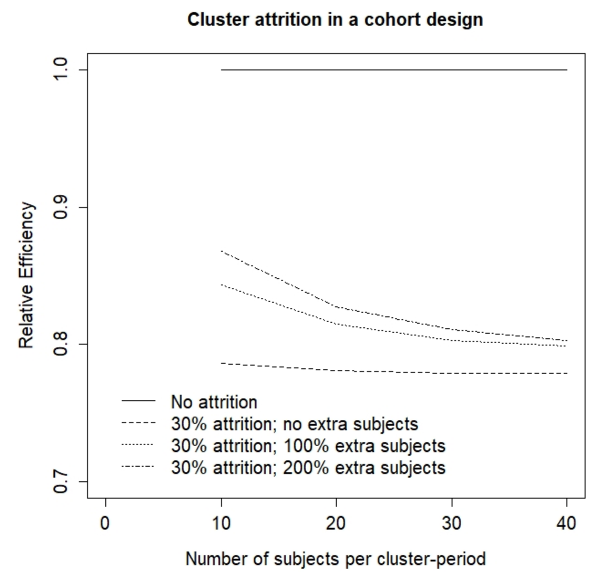


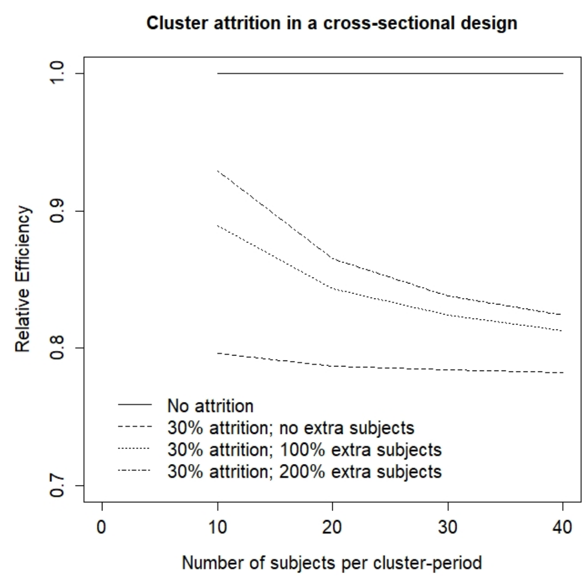
For all graphs

- $\eta = 0.1$
- $\rho = 0.2$
- $\xi = 0.3$

Accounting for unanticipated attrition



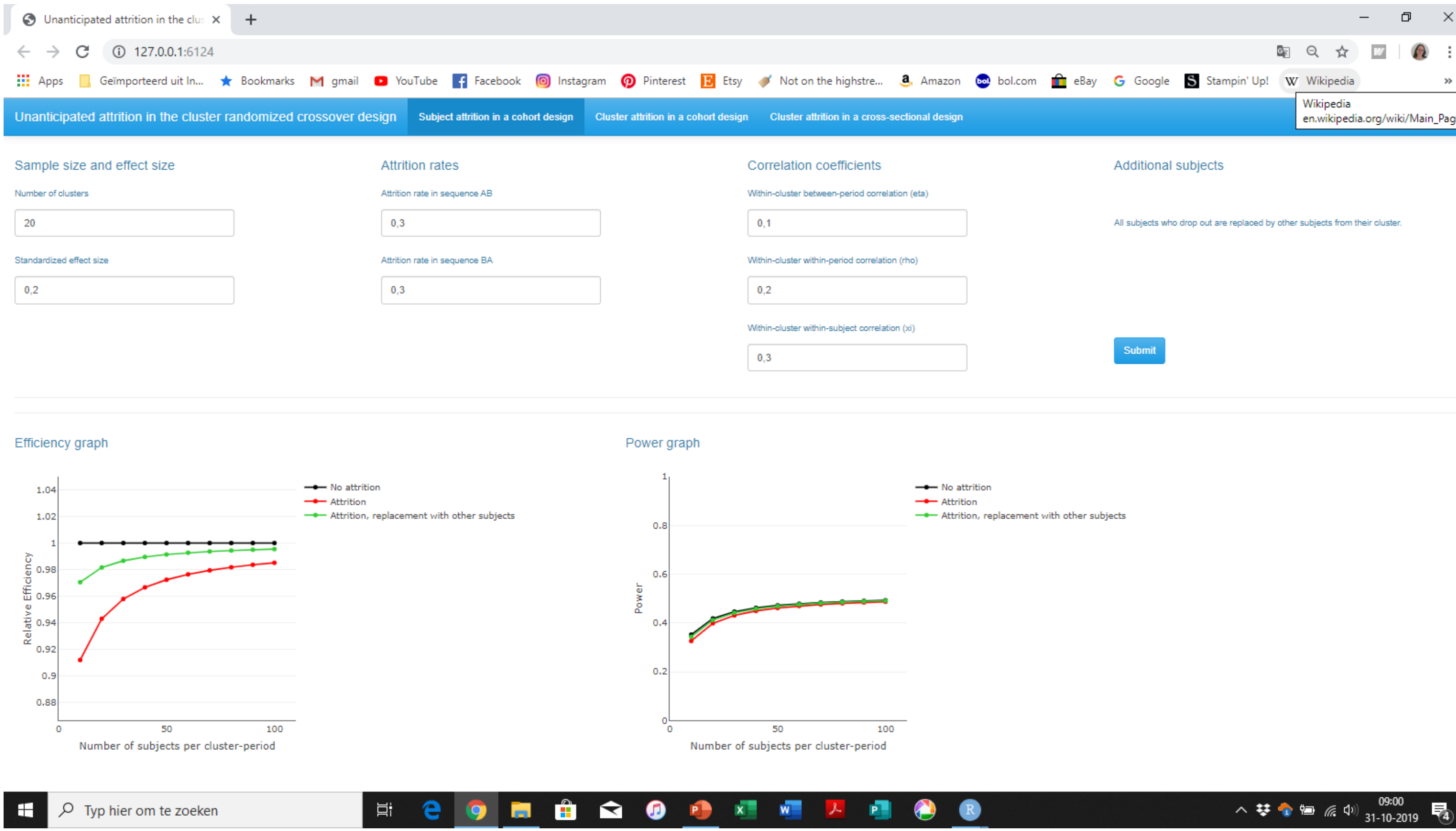




For all graphs

- $\eta = 0.1$
- $\rho = 0.2$
- $\xi = 0.3$

Shiny App



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https://utrecht-university.shinyapps.io/CRXO1
https://utrecht-university.shinyapps.io/CRXO2

Example: lavender scent in dental care

- Kritsidima, Newton and Asimakopoulou (2010)
- Effects of lavender scent on dental patients' anxiety
- 340 patients from one dental
- One of the outcomes was the Modified Dental Anxiety Scale.
- The difference between the two conditions was insignificant ($F(1,338)=2.17$, $p>0.05$). The estimates were: mean= 9.84, SD=4.74 (lavender) and mean=10.65, SD=5.40 (control),
- Hence the effect size was small (Cohen's $d = 0.16$) and a total sample size of 1228 would have been needed to detect such an effect with 80% power in a two-sided test with α=0.05.
- The power for a study with 340 subjects is only 0.31.

Example: lavender scent in dental care

Design	Sample size	Power
Individual randomized trial	$k = 1$ cluster, $n = 340$ subjects per cluster	0.31
	$k = 1$ cluster, $n = 1228$ subjects per cluster	0.80
Cluster randomized trial parallel groups	$k = 20$ clusters, $m = 157$ subjects per cluster	0.80
Cluster randomized trial Crossover, cross-sectional	$k = 20$ clusters, $m = 36$ subjects per cluster-period	0.80
Cluster randomized trial Crossover, cohort	$k = 20$ clusters, $m = 26$ subjects per cluster-period	0.81
Cluster randomized trial	No repair: $k = 20$ clusters, $m = 26$ subjects in cluster-period 1	0.75
Crossover, cohort	Increase m: $k = 20$ clusters, $m = 30$ subjects in cluster-period 1	0.80
25% attrition of subjects	Replacement: $k = 20$ clusters, $m = 26$ subjects per cluster-period	0.79

Discussion and conclusions

- Cluster attrition results in a larger loss of efficiency than subject attrition.
- Attrition may be difficult to account for, especially so for unanticipated attrition
- The effect of attrition of clusters is somewhat larger in a cohort design than in a cross-sectional design
  - but the cohort design may still be more efficient in the case attrition occurs.
- Extensions
  - More treatments, more periods, qualitative outcomes
  - Stepped-wedge design

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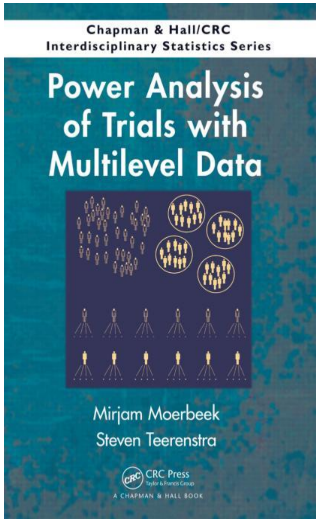
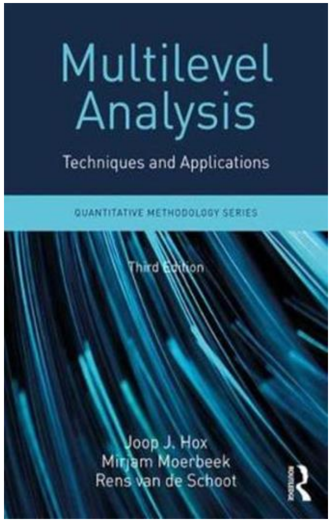
Thank you for your attention!

Are there any questions?

Have you read my books?





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