Between-centre differences in overall patient outcomes and in trial treatment effects in multicentre perioperative trials

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Introduction

- In multicentre trials, patient outcomes have been shown to differ substantially due to differences across centres and/or characteristics of patients treated.
- Most multicentre trials use centre as a stratification variable during randomisation to control for these differences.
- For the analysis, it is recommended that centre is adjusted for, to provide greater statistical power and correct for Type I error rates for the treatment effect.

Aims

We used data from a large multicentre parallel-group two-arm superiority trial in anaesthesia (ENIGMA-II) with randomisation stratified by centre:

- to assess whether there are centre differences in the primary outcome (a composite of death and cardiovascular complications) and hospital length of stay (LOS), and treatment effect, and
- to examine if the heterogeneity affects the overall treatment effect

Methods

- We used random effects logistic (primary outcome) and Weibull (hospital LOS) regression (i) with random intercept for centre (ii) with random intercept for centre and random slope of the treatment effect per centre to estimate the between-centre and treatment effect heterogeneity. For the parametric survival model, the event was hospital discharge, with censoring at 30 days.
- We used random effects meta-analysis (DerSimonian & Laird) to assess heterogeneity of treatment effect between centres.
- We used a non-inferential visual aid by Schou and Marschner to detect treatment effect heterogeneity across centres as a practical addition to a formal test of interaction.
- We used fixed (not adjusted for centre) and random effects logistic and Weibull models (as specified above) and meta-analysis to estimate the treatment effect.

Figure 1: Distribution plot of the centre effect on baseline odds in the control group (patients not receiving nitrous oxide) alongside the centre effect on treatment effect (r* = 1.00, 95% CI: -1.00, 1.00) (left) and observed and expected treatment heterogeneity (right) for the primary outcome

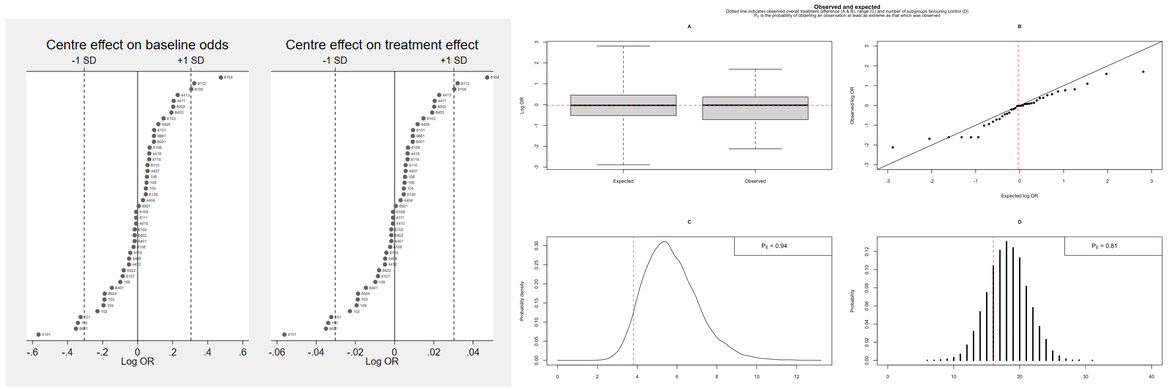
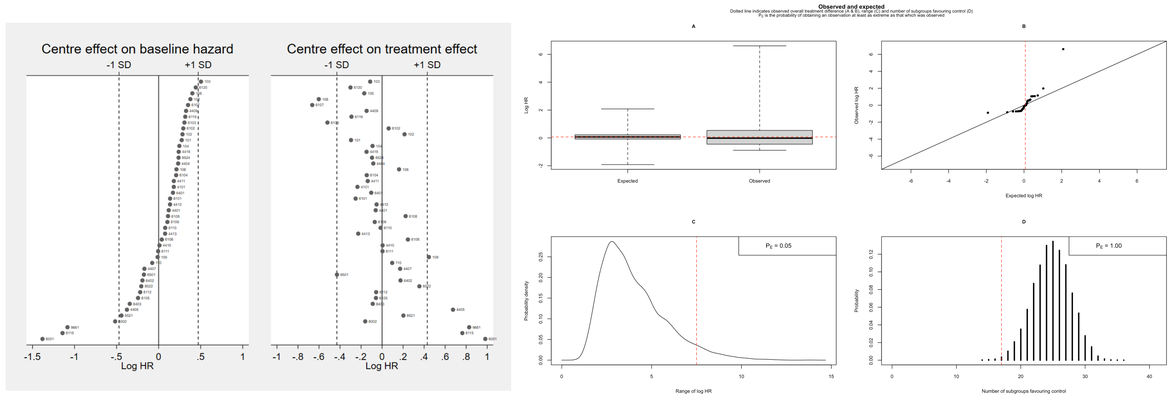


Figure 2: Distribution plot of the centre effect on baseline hazards in the control group (patients not receiving nitrous oxide) alongside the centre effect on treatment effect (r* = -0.73, 95% CI: -0.89, -0.43) (left) and observed and expected treatment heterogeneity (right) for hospital LOS



*r is the correlation between the random intercept and random slope for treatment

Table 1: Estimated treatment effects (95% CI) on the outcomes with different approaches

Model	Primary outcome (Odds Ratio)	Hospital LOS (Hazard Ratio)
Fixed effects regression (not adjusted for centre)	0.96 (0.81, 1.14)	1.07 (1.02, 1.12)
Random effects regression with random intercept for centre	0.96 (0.81, 1.14)	1.07 (1.02, 1.12)
Random effects regression with random intercept for centre and random slope of the treatment effect per centre	0.96 (0.81, 1.14)	1.08 (0.92, 1.27)
Random effects meta-analysis	0.96 (0.81, 1.15)	1.02 (0.88, 1.18)

Results/Discussion

- In the ENIGMA-II trial, there were 7,011 patients from 45 centres. The primary outcome occurred in 283 (8.1%) patients receiving nitrous oxide (intervention) and 296 (8.4%) patients not receiving nitrous oxide (control). The median hospital stay was 6.1 (3.3-10.1) days in both groups.
- There were between-centre differences in both outcomes (**Figures 1 and 2**). There was no important heterogeneity in the primary outcome (I^2 = 0%) and substantial heterogeneity in hospital LOS (I^2 = 82.7%)
- There was a negative correlation between the random effects for hospital LOS, suggesting that a higher baseline hazard is associated with a larger treatment effect in favour of the intervention (**Figure 2**).
- The non-inferential tool by Schou and Marschner indicates that chance variation is plausible for the spread of centre-specific treatment effects for the primary outcome (**Figure 1**). However, for hospital LOS, the observed treatment differences was unusual relative to what would be expected by chance under the assumption of homogeneity (**Figure 2**).
- The treatment effect was similar after adjusting for between-centre differences in outcome and/or between-centre treatment differences, when compared to the model not adjusted for centre (**Table 1**).

Conclusion

In our study, we did not find any support that between-centre differences in outcome or treatment effect affect the overall treatment effect in an RCT.

References

- Myles PS, Leslie K, Chan MTV, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. The Lancet. 2014;384(9952):1446-54.
- Schou IM, Marschner IC. Methods for exploring treatment effect heterogeneity in subgroup analysis: an application to global clinical trials. Pharm Stat. 2015;14(1):44-55.