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Evaluating Amyloid-Beta as a Surrogate Endpoint for Clinical Function in Alzheimer's Disease

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Background

The use of amyloid-beta (Aβ) clearance to support regulatory approvals of drugs in Alzheimer's disease remains controversial. This research aims to evaluate the **surrogate relationship** between **treatment effects on Aβ and clinical function**, measured by Clinical Dementia Rating - Sum Of Boxes (CDR-SOB) using evidence from randomised controlled trials (RCTs) of anti-Aβ monoclonal antibodies (MABs).

Methods

Data from RCTs reporting treatment effects on Aβ levels and CDR-SOB of MABs were identified through literature review. A **Bayesian meta-analysis model[1]** was applied, with the intercept, slope and conditional variance parameters quantifying the association. The surrogate relationship for individual treatments was evaluated using **subgroup analyses and hierarchical models[2,3]** to borrow information across treatments.

Figure 1: The criteria set out by Daniels & Hughes[1] on a perfect surrogate relationship

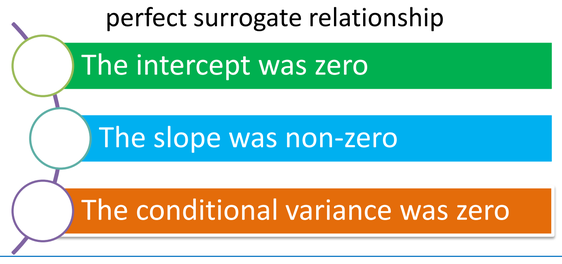
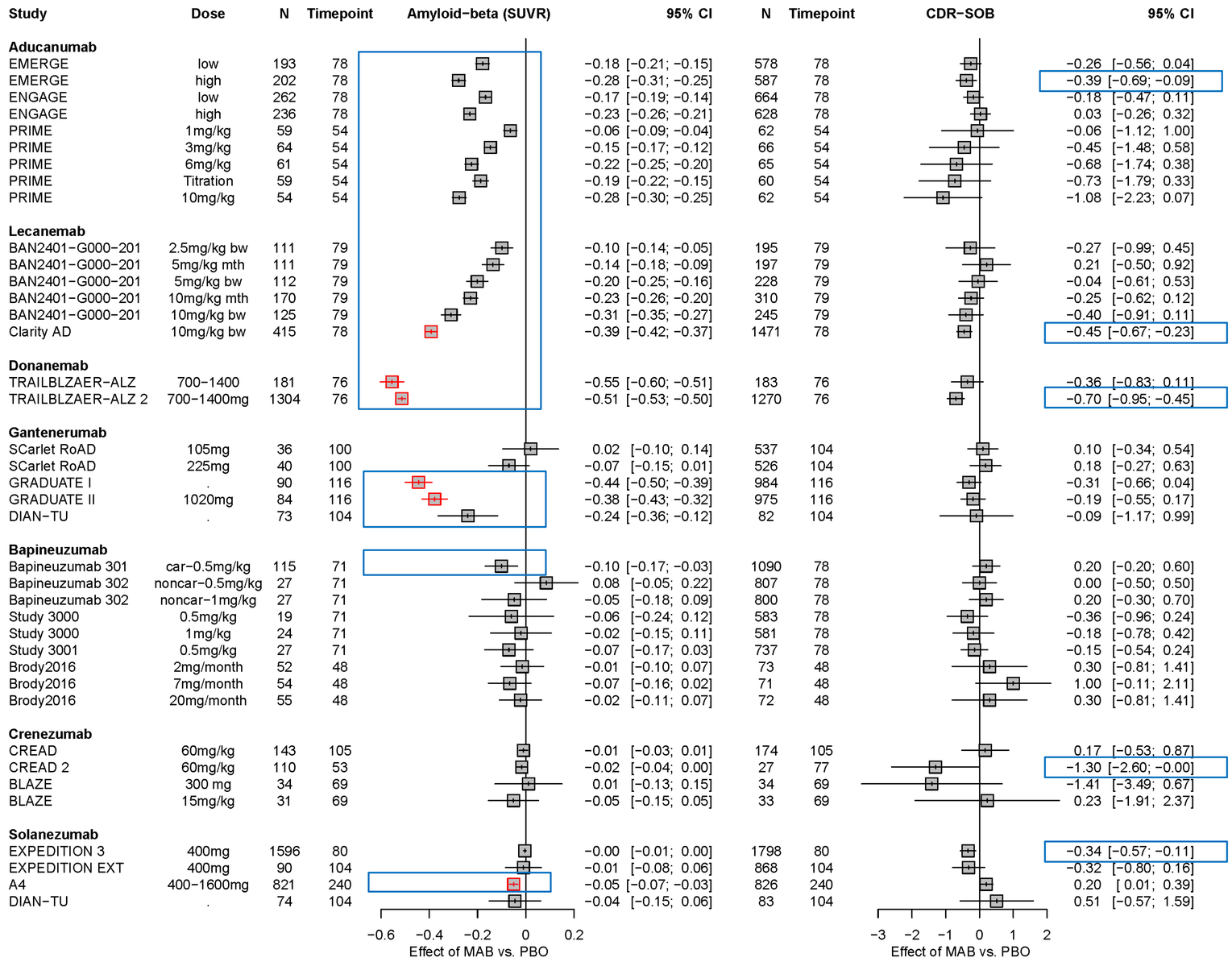
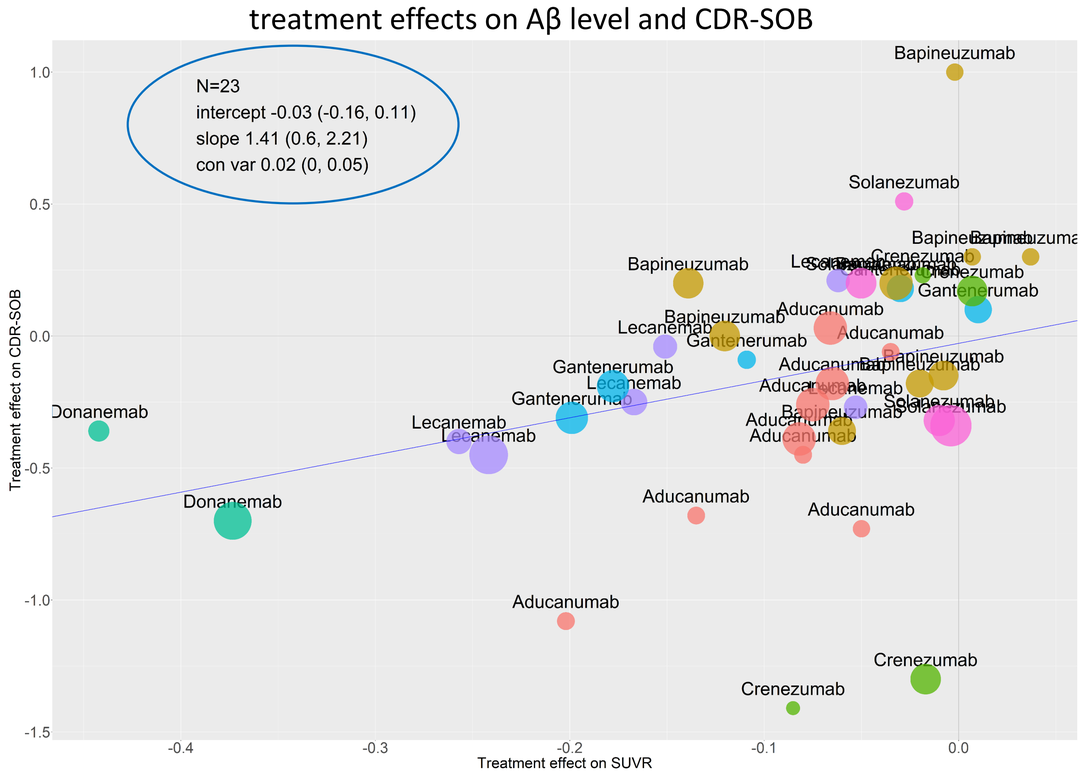


Figure 2: Forest plot illustrating the treatment effects of MABs versus placebo (PBO) on Aβ level and CDR-SOB



The timepoint is in weeks and the treatment effect is measured by the difference in change from baseline to the follow-up time point vs. placebo (PBO). Estimates in red were imputed by applying a conversion formula based on the radioactive tracer used in the PET scan, where the effect on amyloid-beta was reported on the Centiloid scale alone.

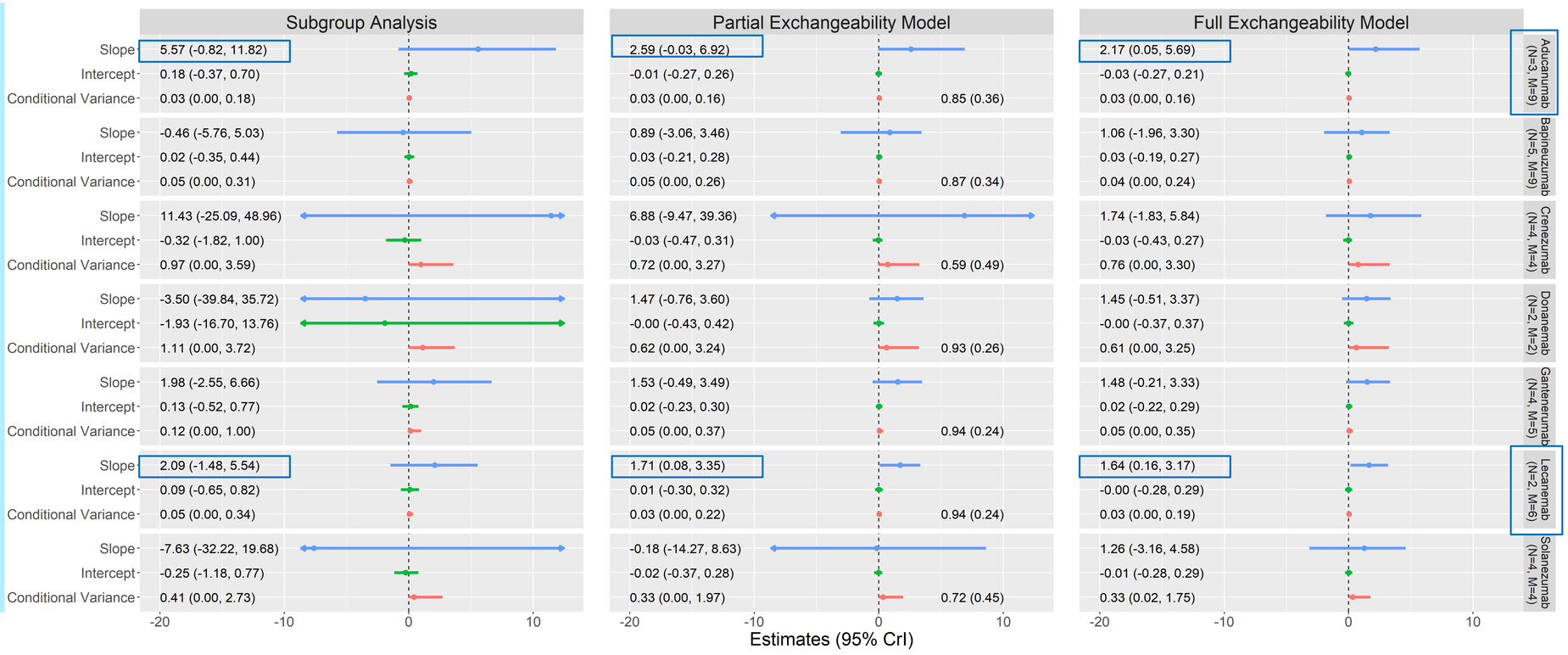
Figure 3: Bubble plot of the overall surrogate relationship between treatment effects on Aβ level and CDR-SOB



Results

1. The review identified **23 RCTs with 39 treatment contrasts** (Figure 2) for seven MABs, including aducanumab, bapineuzumab, crenezumab, donanemab, gantenerumab, lecanemab and solanezumab.
2. The overall surrogate relationship (Figure 3) between treatment effects on Aβ level (on the standardised uptake value ratio scale) and CDR-SOB across all MABs was strong: with the **close to zero intercept** at -0.03 (95% CrI: -0.16, 0.11), **a positive slope** of 1.41 (95% CrI: 0.6, 2.21) and **a small conditional variance** of 0.02 (95% CrI: 0, 0.05).
3. The results showed large uncertainty around the surrogacy parameters for individual treatments (Figure 4). The use of **the hierarchical model reduced the uncertainty** around the key parameters. The reduction in the width of CrI was 71% (51%-95%) for slope and 28% (7%-65%) for conditional variance, when comparing results from the full-exchangeability model with subgroup analyses.

Figure 4: Forest plot of estimates of slope, intercept and conditional variance for the evaluation of individual surrogate relationship between treatment effects on Aβ level and CDR-SOB



Conclusions

1. The effect on Aβ level was **a good surrogate endpoint** for the effect on CDR-SOB when assuming **a common surrogate relationship** across all included treatments.
2. Surrogate relationships were **uncertain for individual treatments**, but the uncertainty was largely reduced when borrowing information from other treatments in the hierarchical models.
3. Aβ reduction could potentially serve as a surrogate endpoint for clinical efficacy, thereby **accelerating the evaluation** of novel therapies.

References

[1] Daniels and Hughes (1997): Meta-analysis for the evaluation of potential surrogate markers. Statistics in Medicine.
[2] Bujkiewicz *et al.* (2019): NICE DSU Technical Support Document 20: Multivariate meta-analysis of summary data for combining treatment effects on correlated outcomes and evaluating surrogate endpoints.
[3] Papanikos *et al.* (2020): Bayesian hierarchical meta-analytic methods for modelling surrogate relationships that vary across treatment classes using aggregate data. Statistics in Medicine.
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