

Optimizing assay sensitivity by combining highly variable pain subjects' exclusion with adjusted analysis.

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Introduction and Motivation

The baseline pain variability (BPV) has often been presented as

- positively correlating with the placebo response
- associated with a lack of consistency in the subjects' pain evaluation.

Enrichment based on the exclusion of the high BPV subjects is therefore often advised to improve the precision of the treatment response.

Another common method to increase the assay sensitivity is to adjust the analysis for covariates associated with the response.

We aimed here to study the optimization of the assay sensitivity by combining these two methods.

Study Designs and Patients

This analysis used the data of 171 subjects with moderate to severe painful knee OA.

All the subjects participated in the same randomized, double-blind, and placebo-controlled clinical trial.

Method

The **baseline pain variability (BPV)** was evaluated in this analysis by computing the standard deviation of the daily Average Pain Scores (APS) reported during the last week of the baseline period.

To evaluate the potential impact of an enrichment on the treatment effect precision, **up to 25% of the subjects** with the highest BPV **were excluded**.

This method was used in combination with the **adjustment for a predictive placebo covariate**. We used here the Placebell covariate, predictive of the placebo response. This covariate is computed with patients' baseline characteristics (traits of personality, demographics, history, variability and severity of disease).

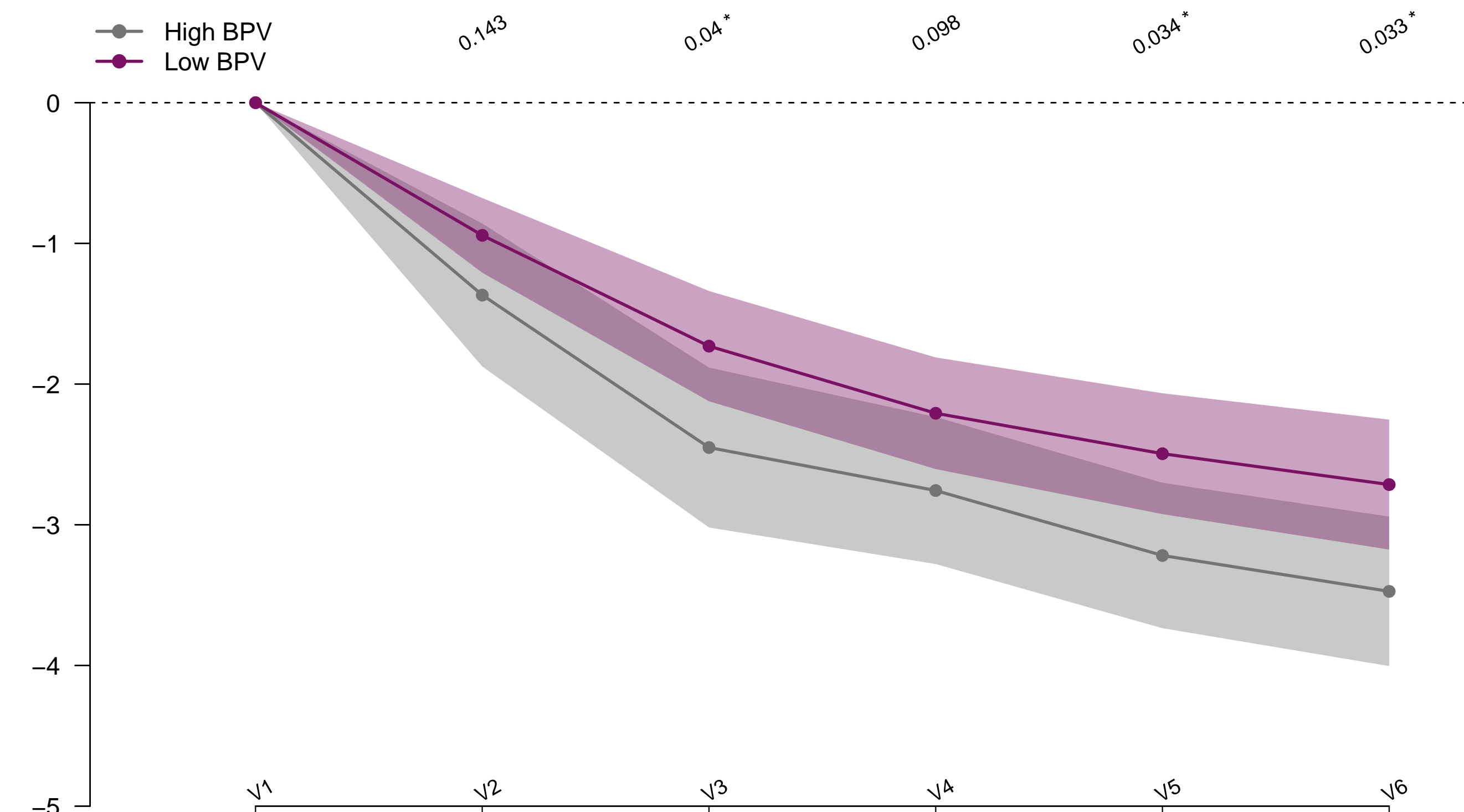
The impact on the assay sensitivity of the different combinations was assessed by computing the change in precision. This **precision** was computed using

$$p = \frac{N}{S_{\text{endpoint}}^2}$$

where p is the precision, S_{endpoint}^2 is the variance of the endpoint and N is number of subjects. To simulate the replacement in an enrichment procedure, N was fixed and equal to 171 in all the computations.

Baseline Pain Variability

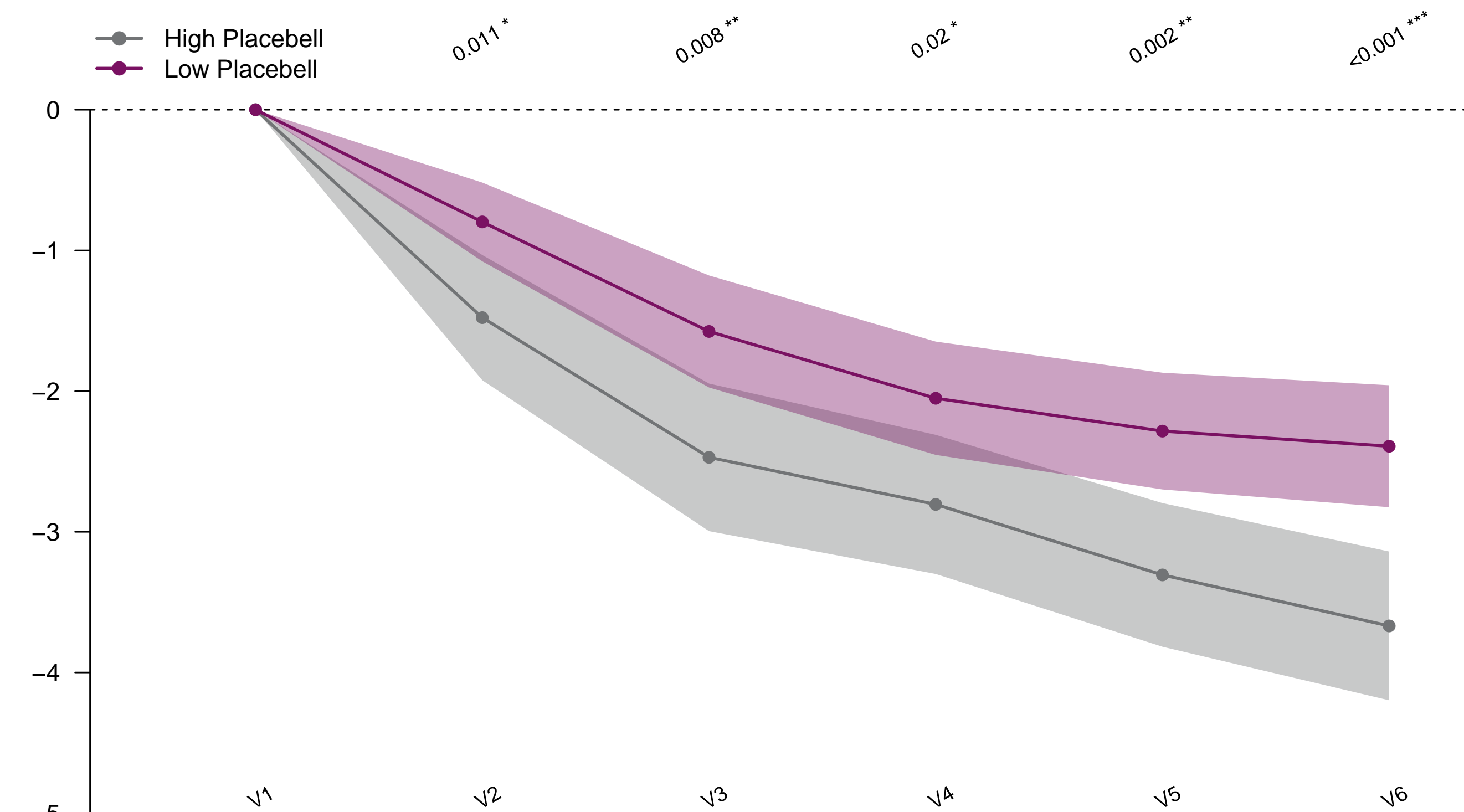
Figure 1: Change from baseline of the APS, for the subjects with the highest and the lowest BPV.



BPV was positively correlated with the response (Pearson's $r = 0.21$). The subjects with the highest BPV (bigger than the mean value) have therefore a higher response than the subjects with the lowest BPV (smaller than the mean value).

Placebo Covariate

Figure 2: Change from baseline of the APS, for the subjects with the highest and the lowest Placebell score.

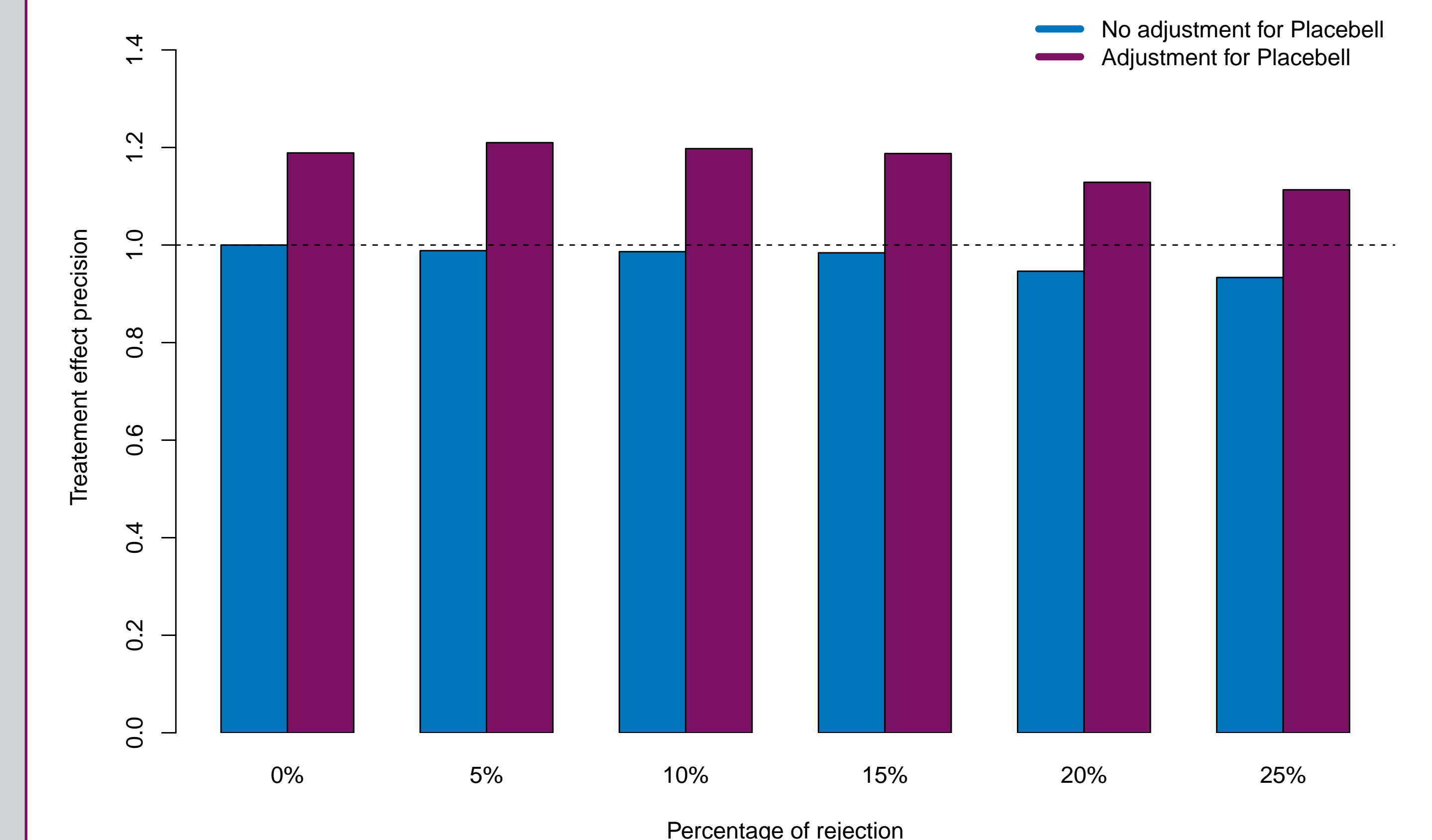


Placebell was positively correlated with the response (Pearson's $r = 0.40$).

The subjects predicted as the highest responders have a higher response.

Treatment response precision

Figure 3: The change in precision of the APS endpoint are compared for the two procedures (with and without Placebell adjustment) and for several proportion of subjects exclusion for the enrichment procedure.



For each procedure (■, ■), increasing the proportion of excluded subjects didn't increase the precision. The precision for enriched populations was even often lower than the precision without enrichment.

For each proportion of exclusion, the precision was always better with the adjustment for Placebell (■) than without (■).

There is no sign of synergistic effect while combining the two methods. As there is no antagonistic effect while combining the two methods, they can be used in combination.

These results were consistent for all the endpoints of the study.

Conclusions

- **Enrichment** based on the replacement of the subjects with the highest Baseline Pain Variability **and adjustment** for Placebell covariate **can be used in combination** to improve the assay sensitivity.
- **The enrichment didn't show a big impact on the precision** on the treatment response of this study.
- Adjustment with the **Placebell covariate outperformed enrichment** both in precision and power.