Reanalysis of ACTT-1 using a Bayesian first-order Markov state transition model for ordinal outcomes

Maximilian Rohde

August 30, 2021

Vanderbilt Department of Biostatistics

Background

ACTT-1 Background

ACTT-1 was a double-blind, placebo-controlled, randomized trial conducted to assess the efficacy of remdesivir for the treatment of COVID-19.

- 541 subjects assigned to remdesivir.
- 521 subjects assigned to placebo.

Patient status was assessed daily for 28 days using an 8-point ordinal scale (see next slide).

Due to enrollment criteria, only states of 4,5,6, and 7 were represented at baseline.

Outcome scale used in ACTT-1

1. Not hospitalized and no limitations of activities
2. Not hospitalized, with limitation of activities, home oxygen requirement, or both
3. Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons)
4. Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care related to Covid-19 or to other medical conditions
5. Hospitalized, requiring any supplemental oxygen
6. Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices
7. Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8. Death

Original analysis in NEJM

RESULTS

A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).

Figure 1: Main results from the original analysis in the New England Journal of Medicine.

Statistical modeling

The data were fit with a Bayesian proportional odds model where the ordinal outcome *y* was predicted by:

- `yprev` : the patient's state from the previous day
- `tx` : the assigned treatment
- `day` : the current study day (using a restricted cubic spline)
- `age` : the age of the patient (using a restricted cubic spline)
- `tx * day` : treatment / age interaction

The model was fit allowing non-PO only for time, with the constraint is that the departure from PO is linear in `y`. Even though the main time effect is nonlinear, using a restricted cubic spline, the non-PO effect is for linear time.

4,000 posterior draws were obtained using MCMC sampling with `Stan`.

Statistical modeling

We model the transition probabilities, conditional on the covariates.

However, we can obtain the unconditional probability of being in state $Y = y$ on day $t \in \{1, 2, \ldots 28\}$.

R code using `rmsb`

```
blrm(Ocens(yl, yu) ~ yprev + rcs(day, 4) * tx + rcs(age, 5),
     ~ day, cppo = function(y) y, data=a, file='bppodc_ppo.rds')
```

Figure 2: R code for model fitting using the `rmsb` package

Time at home

A convenient model-derived quantity to measure treatment efficacy is **mean number of days at home**. Using the ordinal scale defined previously, this is mean time spent in states 1 or 2.

Presenting mean number of days at home can be more interpretable to clinicians.

It also has the benefit of being a single number summary that averages over all the days of treatment.

Time at home

Let $P_t\left(Y = y\right)$ be the probability of being in state y on day t. Then we can define the mean number of days at home as

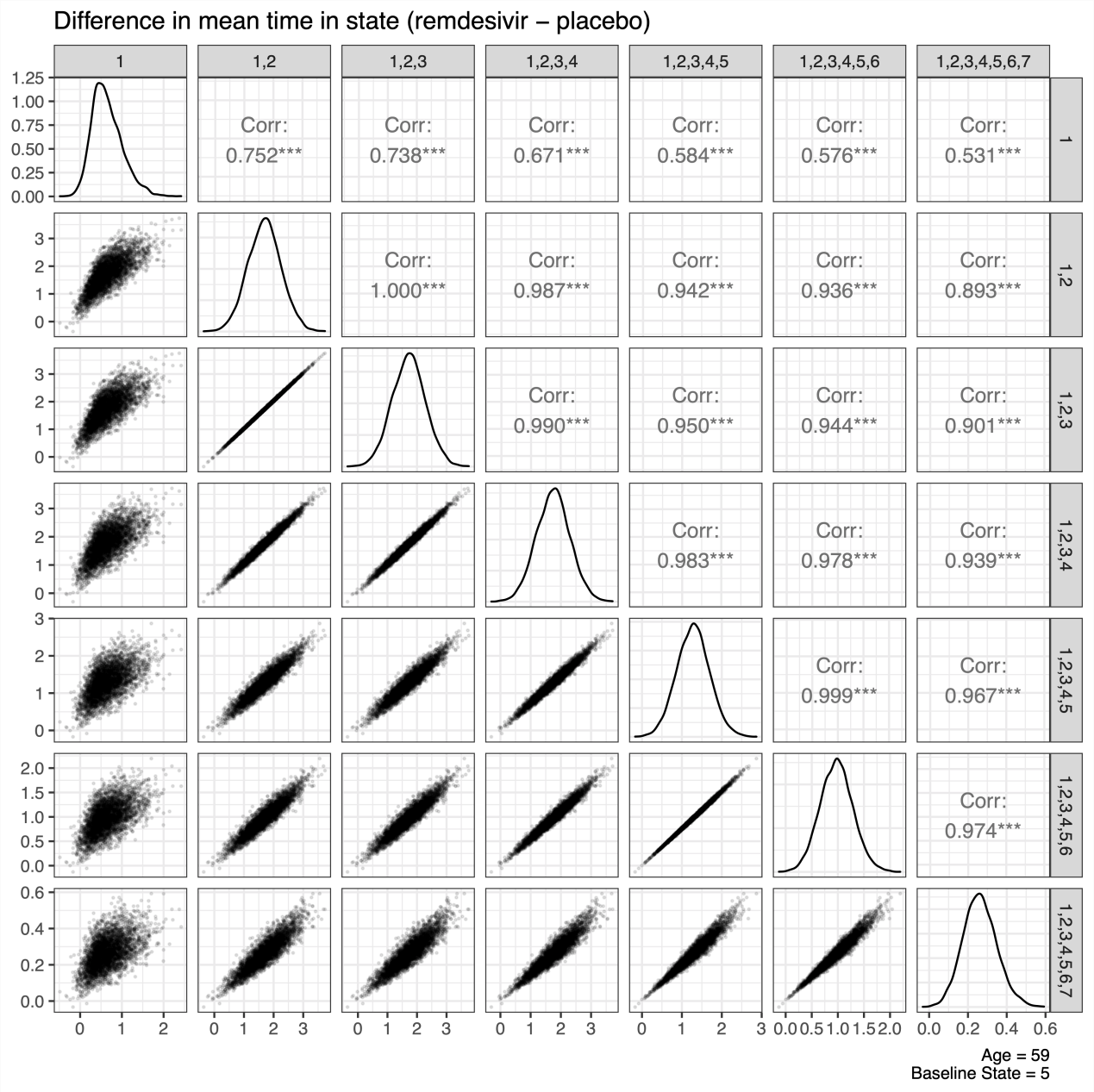
$$\sum_t P_t\left(Y = 1\right) + \sum_t P_t\left(Y = 2\right) \quad \text{where } t \in \{1, 2, 3, \ldots, 27, 28\}$$

We have the data to compute this quantity in ACTT-1 because the ordinal outcome was assessed daily. In studies where this is not the case, we can use linear interpolation to compute the missing values of $P_t\left(Y = y\right)$.

Uncertainty about mean number of days at home can be quantified using the posterior draws obtained when fitting the model.

Results

Different definitions for mean time in state provide redundant information



Probability of benefit (varying baseline state)

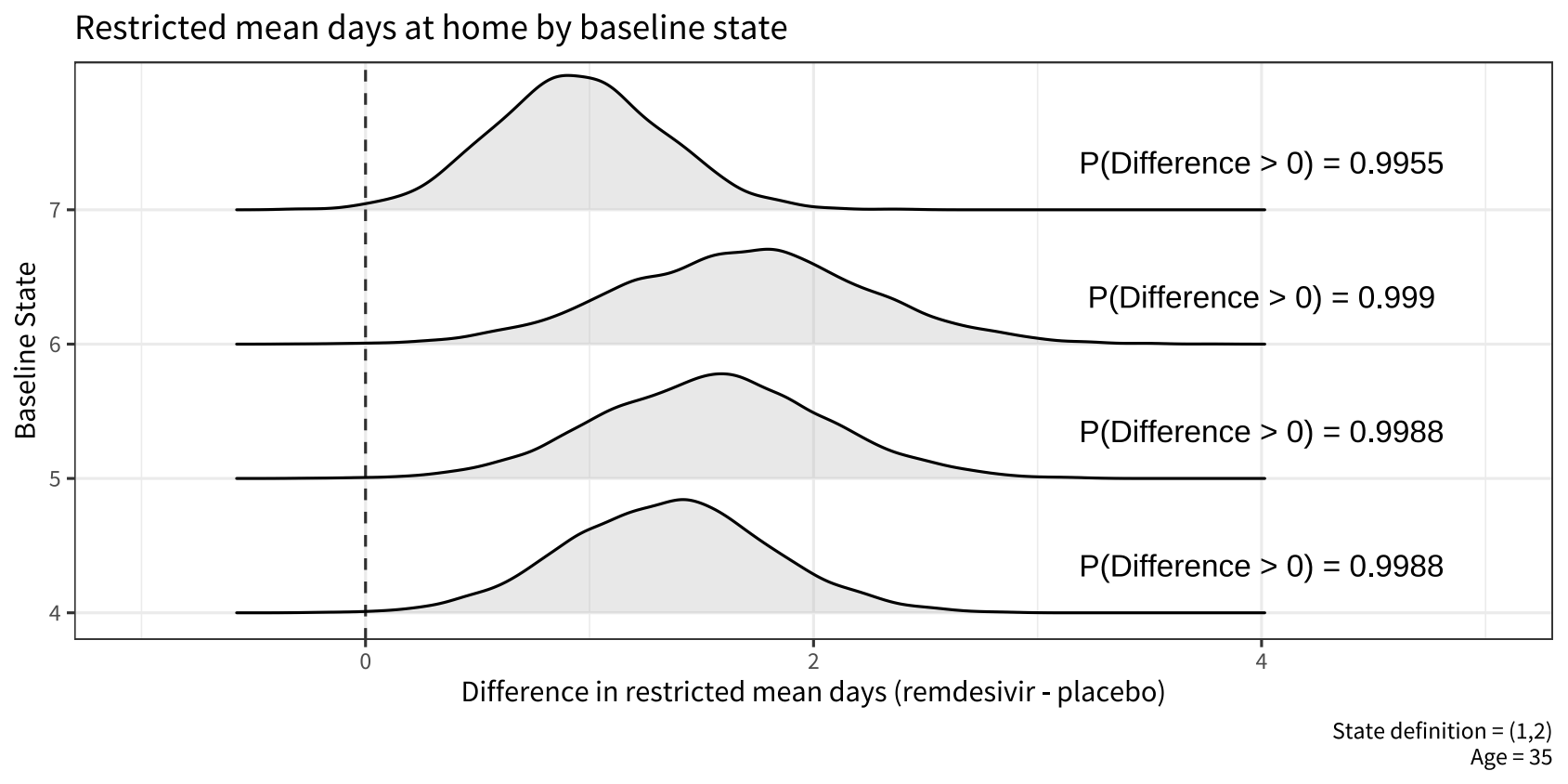


Figure 3: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on age = 35.

Probability of benefit (varying baseline state)

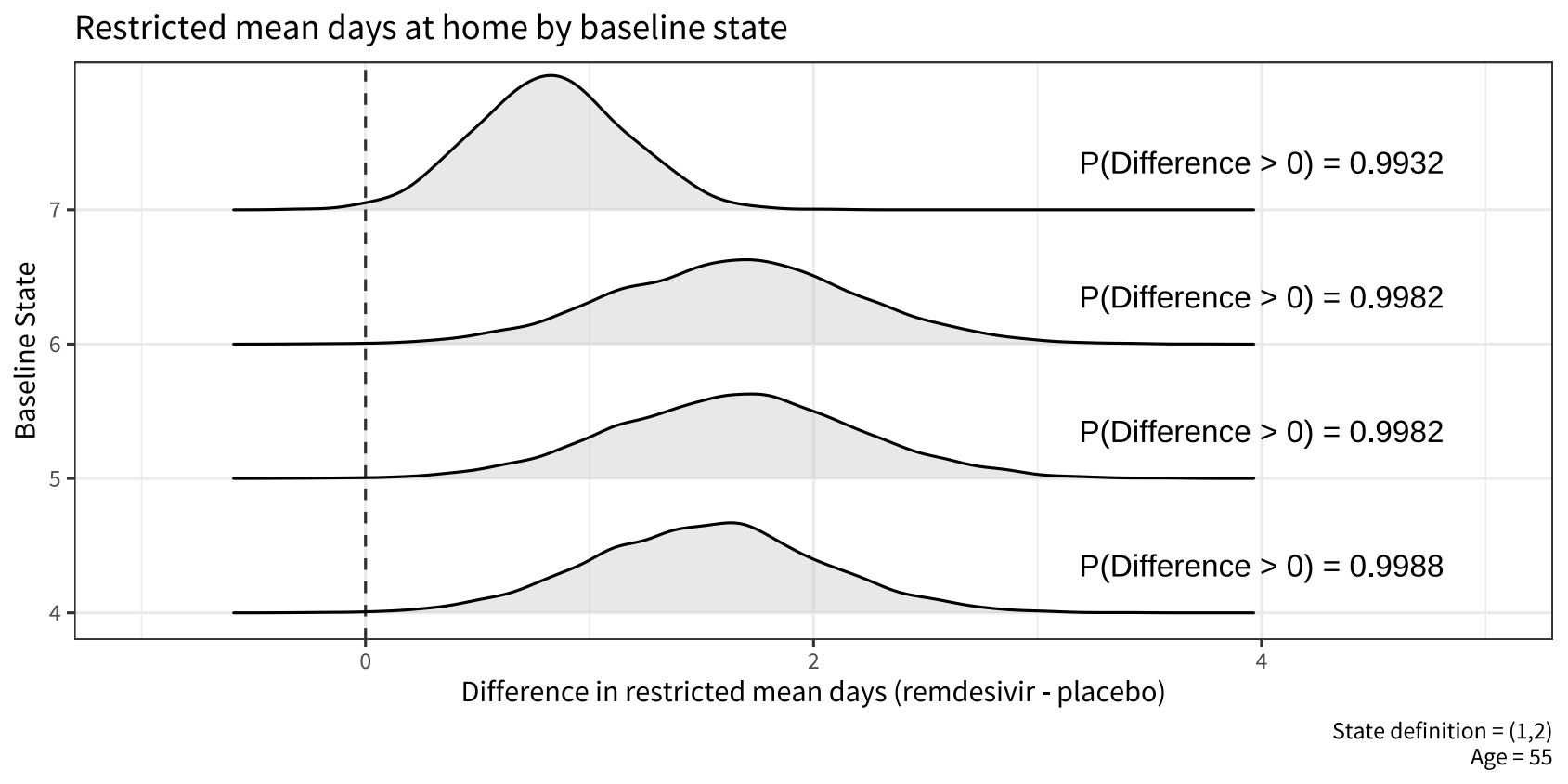


Figure 4: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on age = 55.

Probability of benefit (varying baseline state)

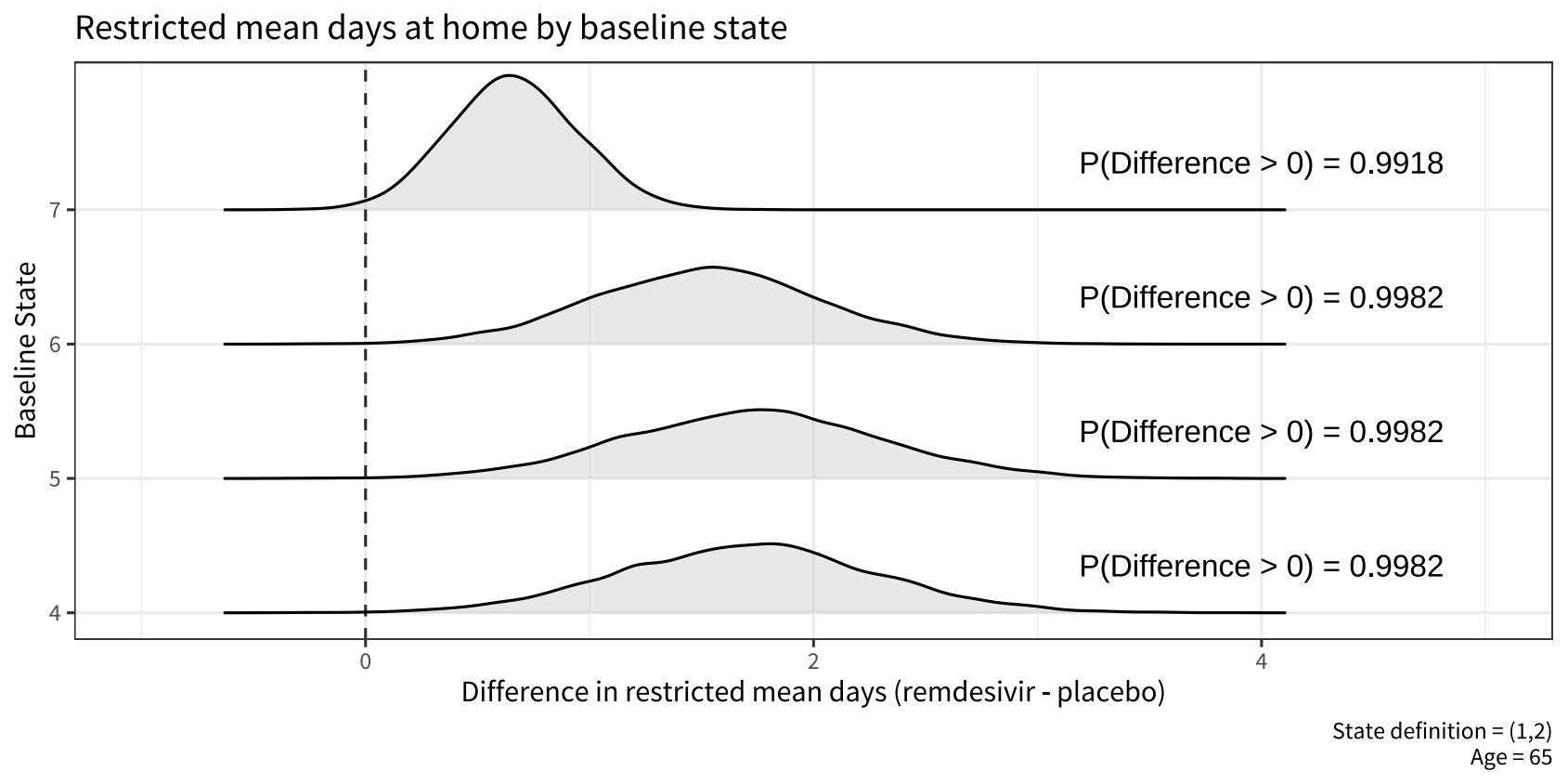


Figure 5: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on age = 65.

Probability of benefit (varying baseline state)

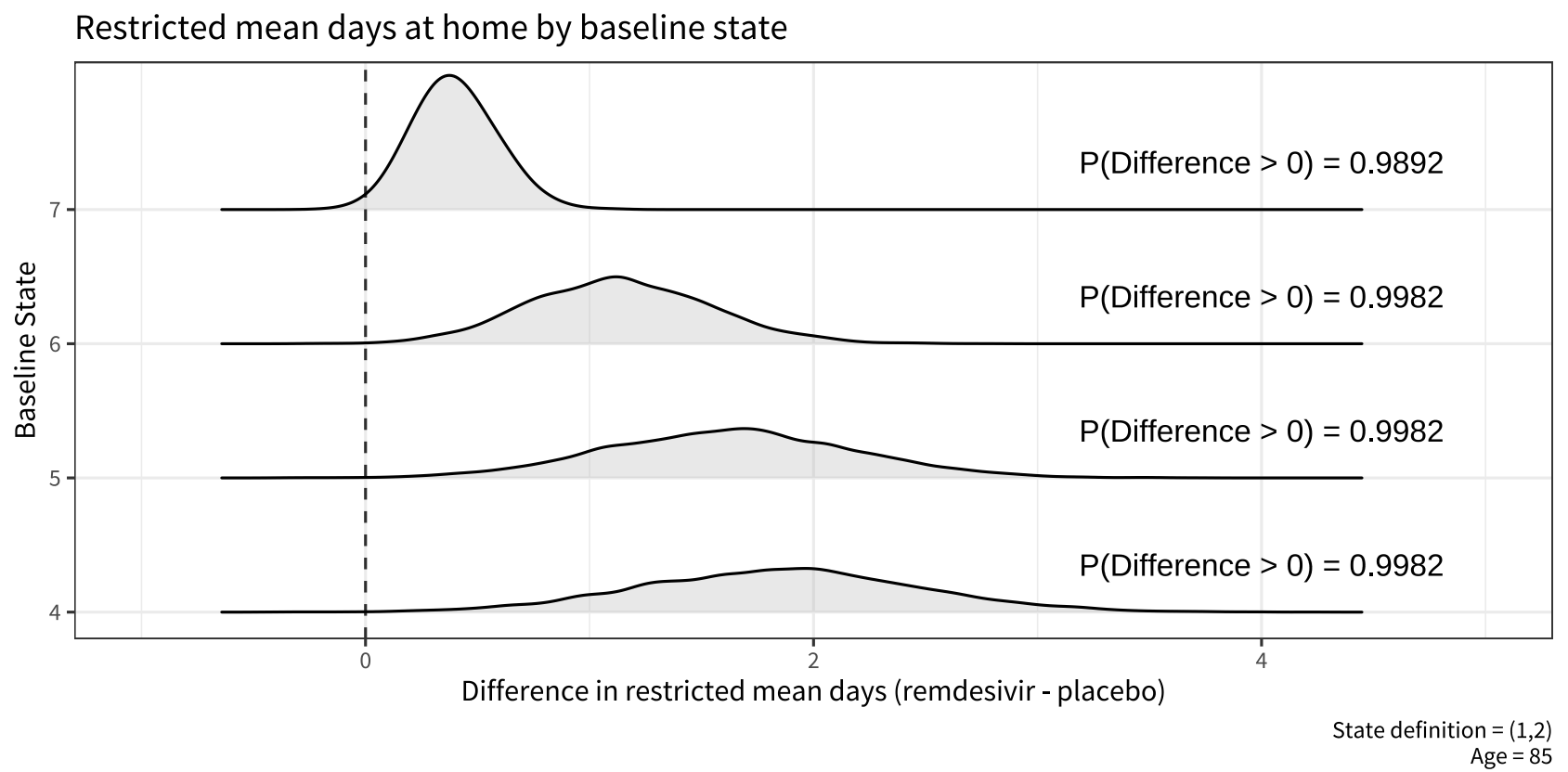


Figure 6: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on age = 85.

Probability of benefit (varying baseline age)

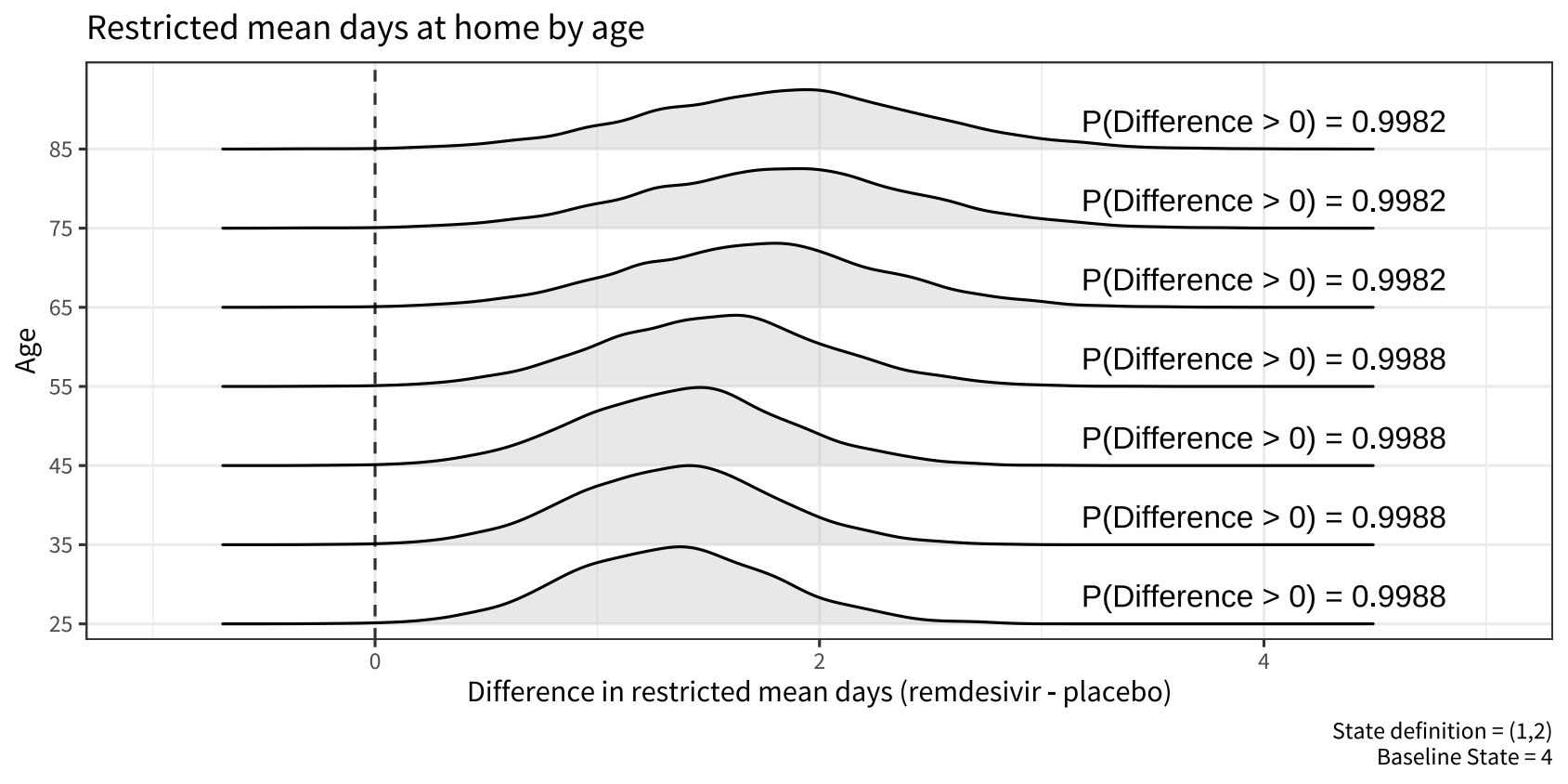


Figure 7: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on baseline state = 4.

Probability of benefit (varying baseline age)

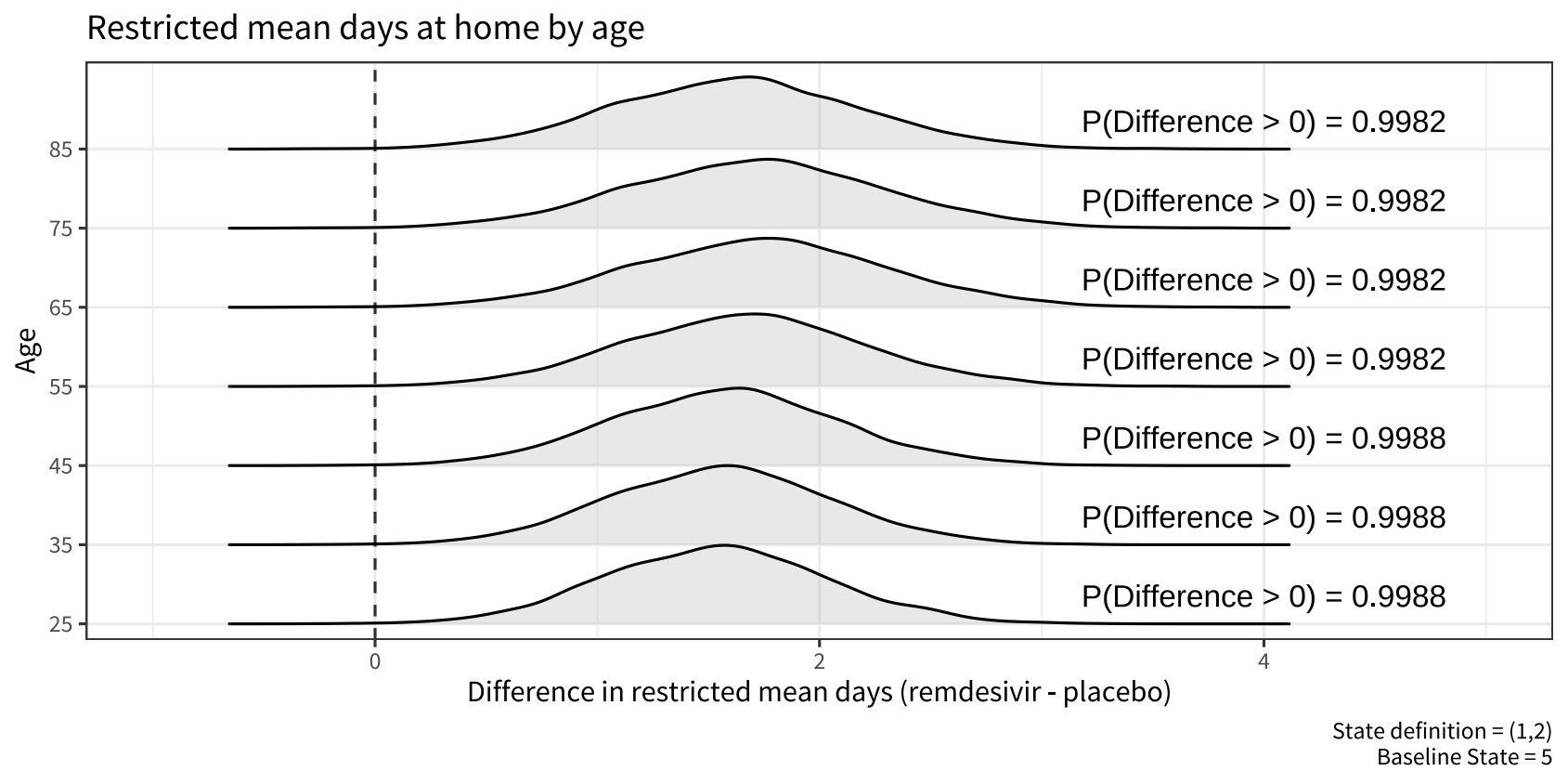


Figure 8: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on baseline state = 5.

Probability of benefit (varying baseline age)

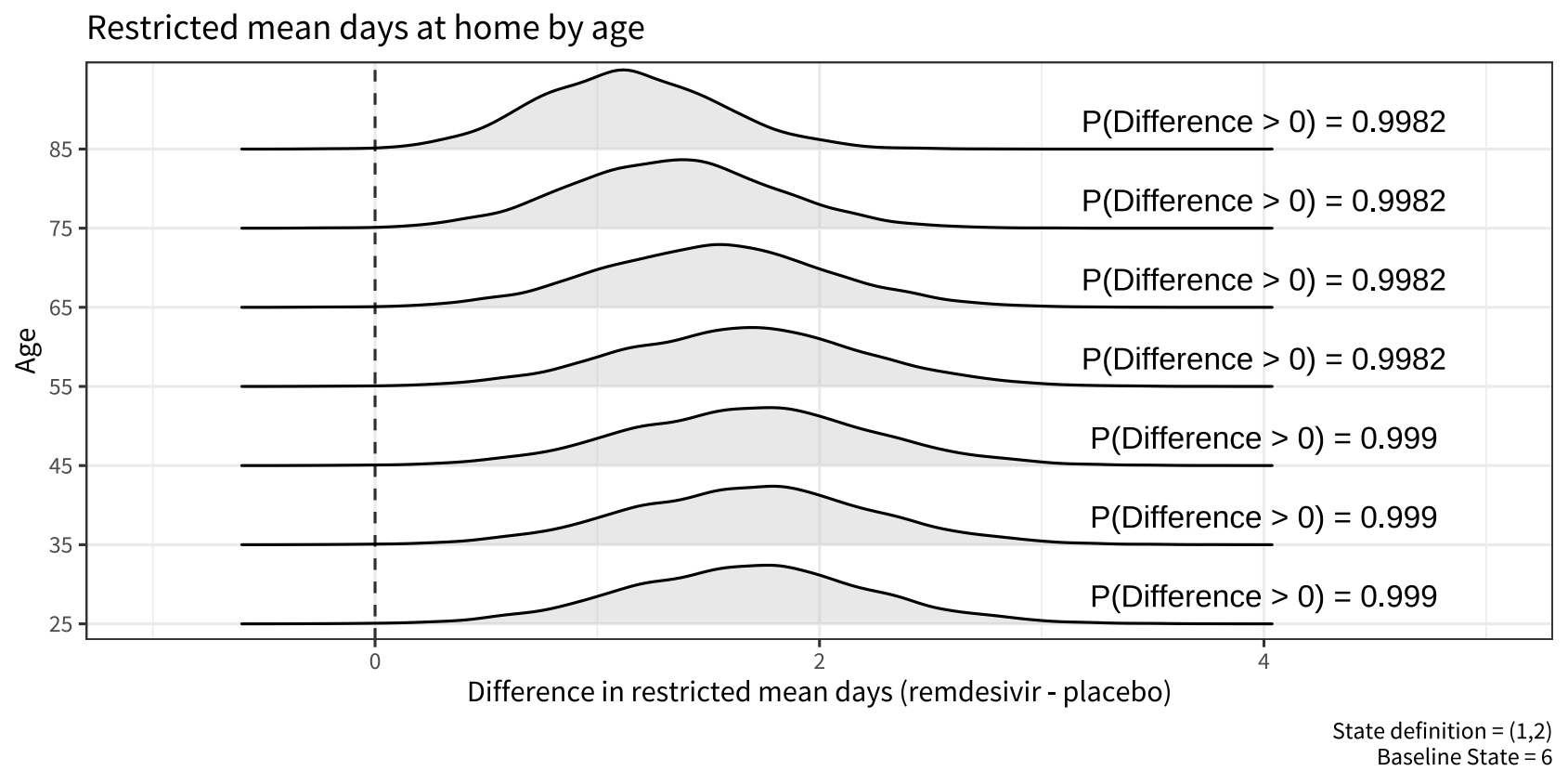


Figure 9: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on baseline state = 6.

Probability of benefit (varying baseline age)

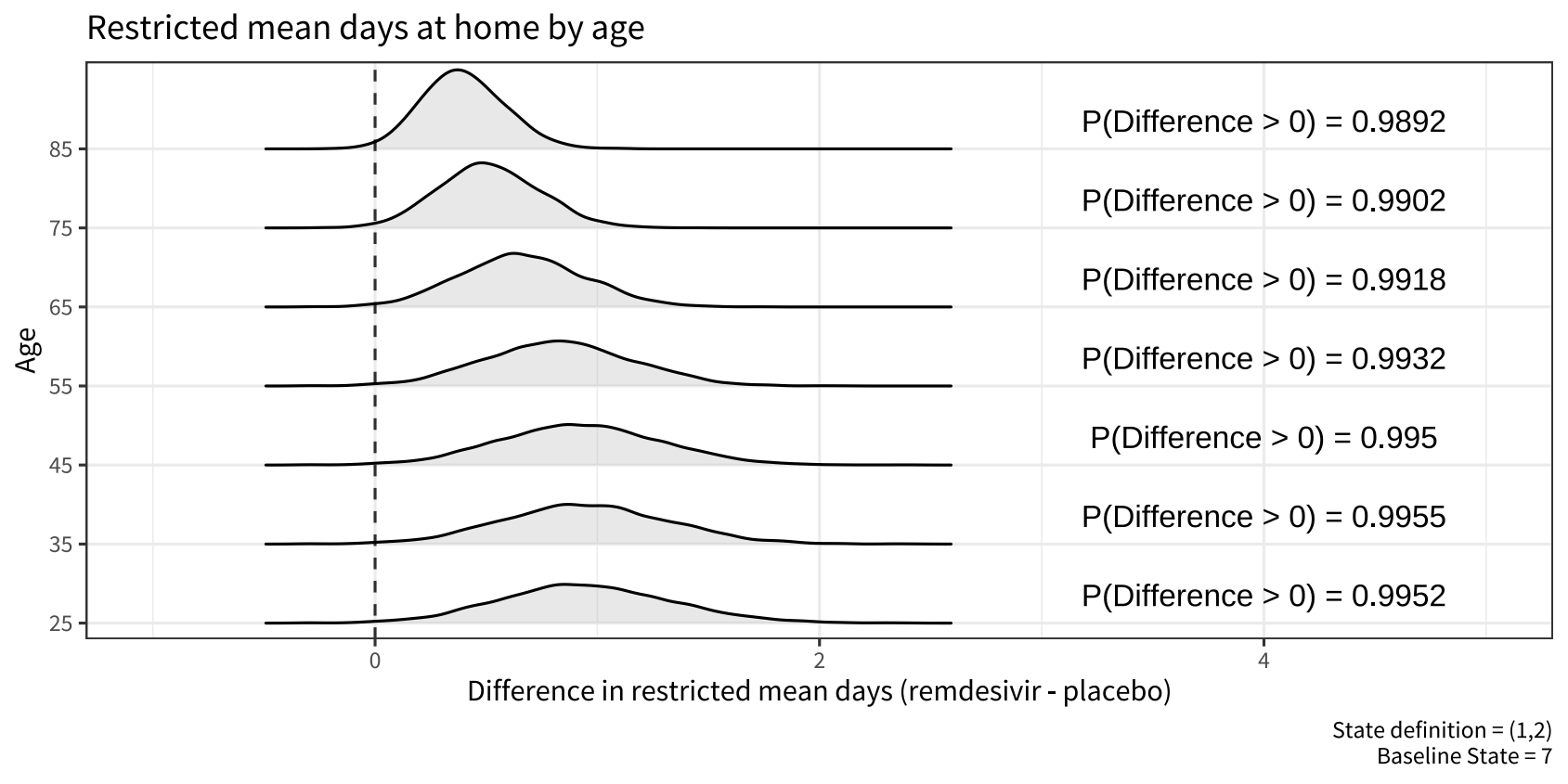


Figure 10: Posterior density for difference between mean days at home for Remdesivir and mean days at home for Placebo, conditional on baseline state = 7.

Probability of benefit (heatmap)

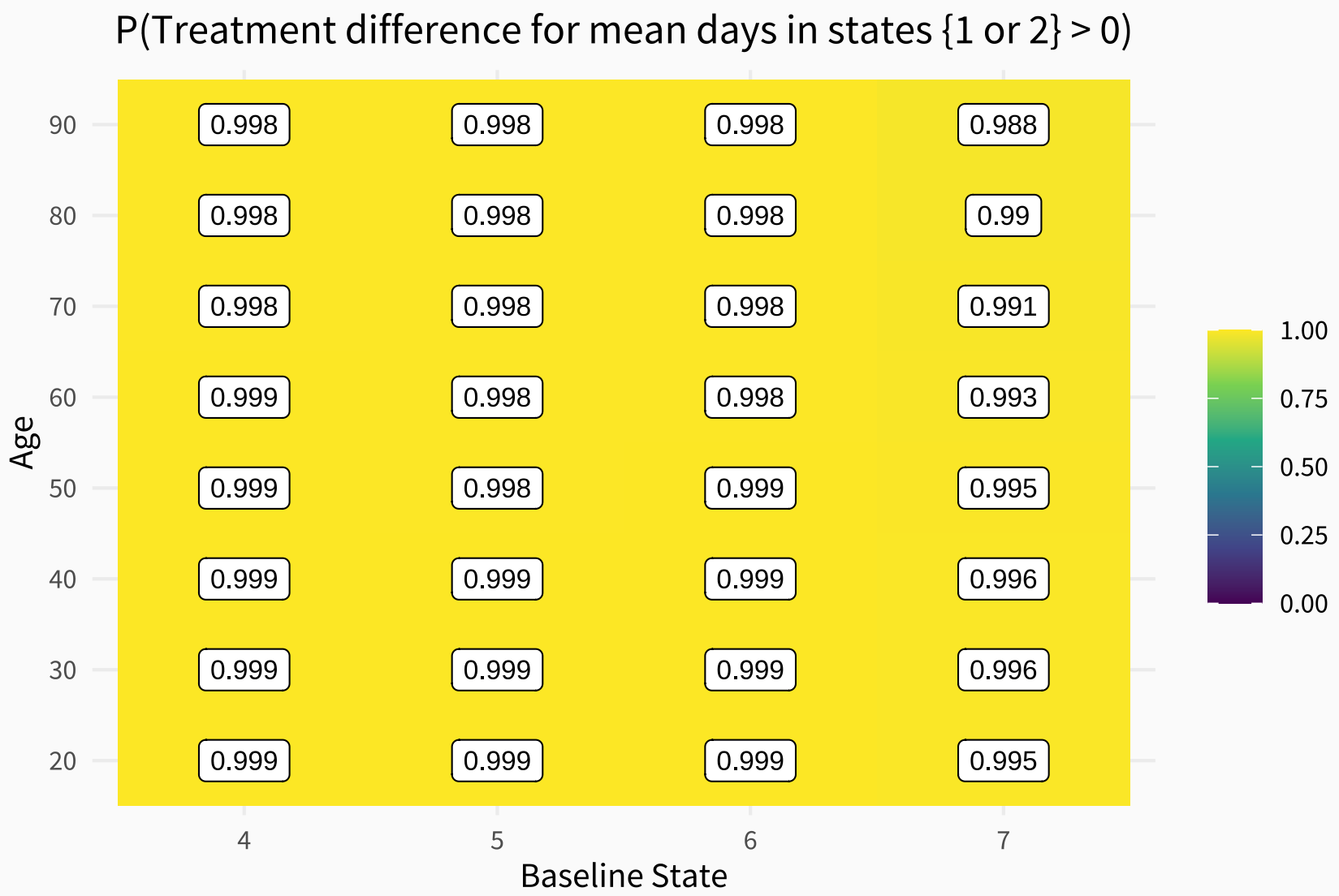


Figure 11: Probability that treatment difference is greater than 0 days at home for various covariates.

Probability of benefit (heatmap)

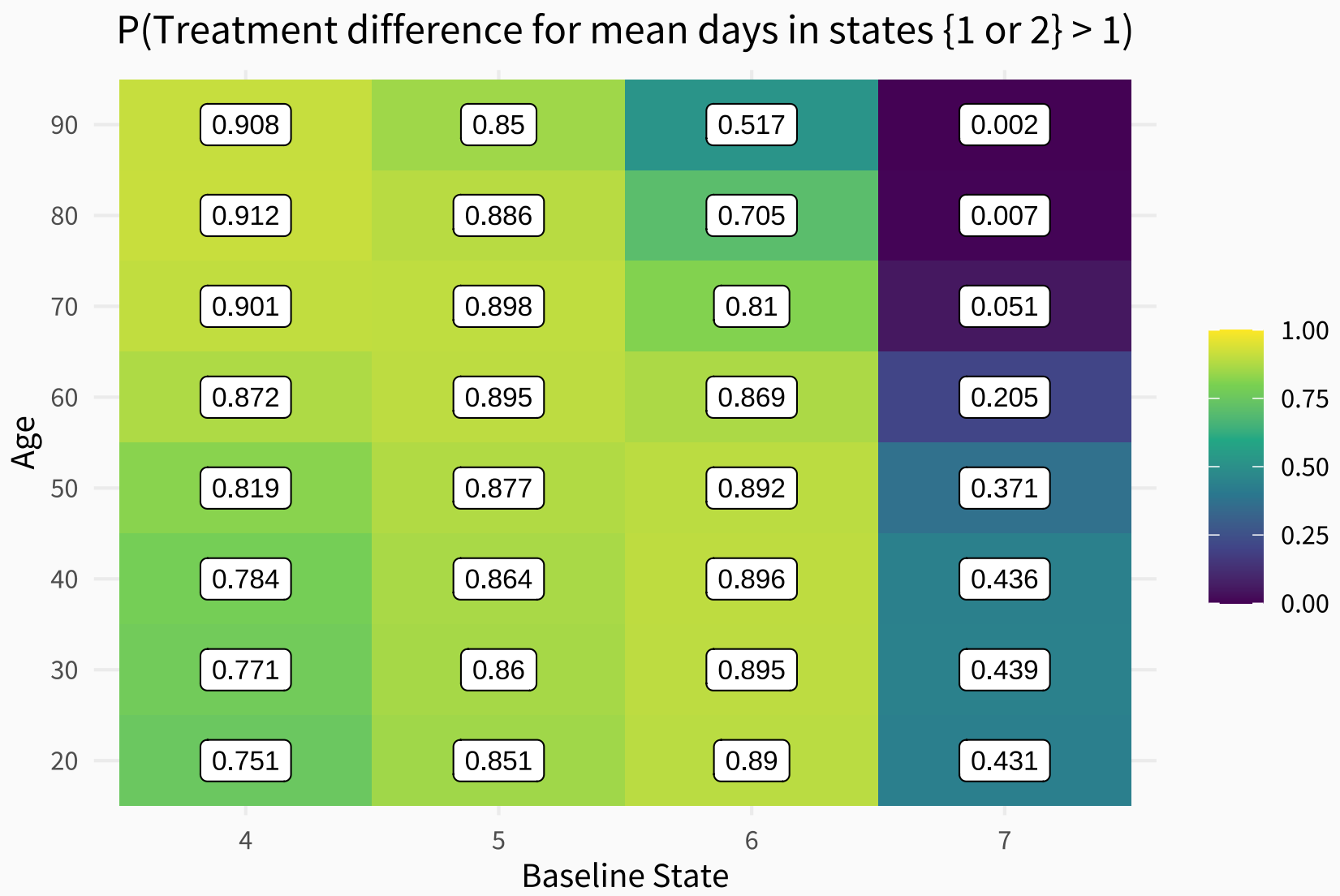


Figure 12: Probability that treatment difference is greater than 1 day at home for various covariates.

Probability of benefit (heatmap)

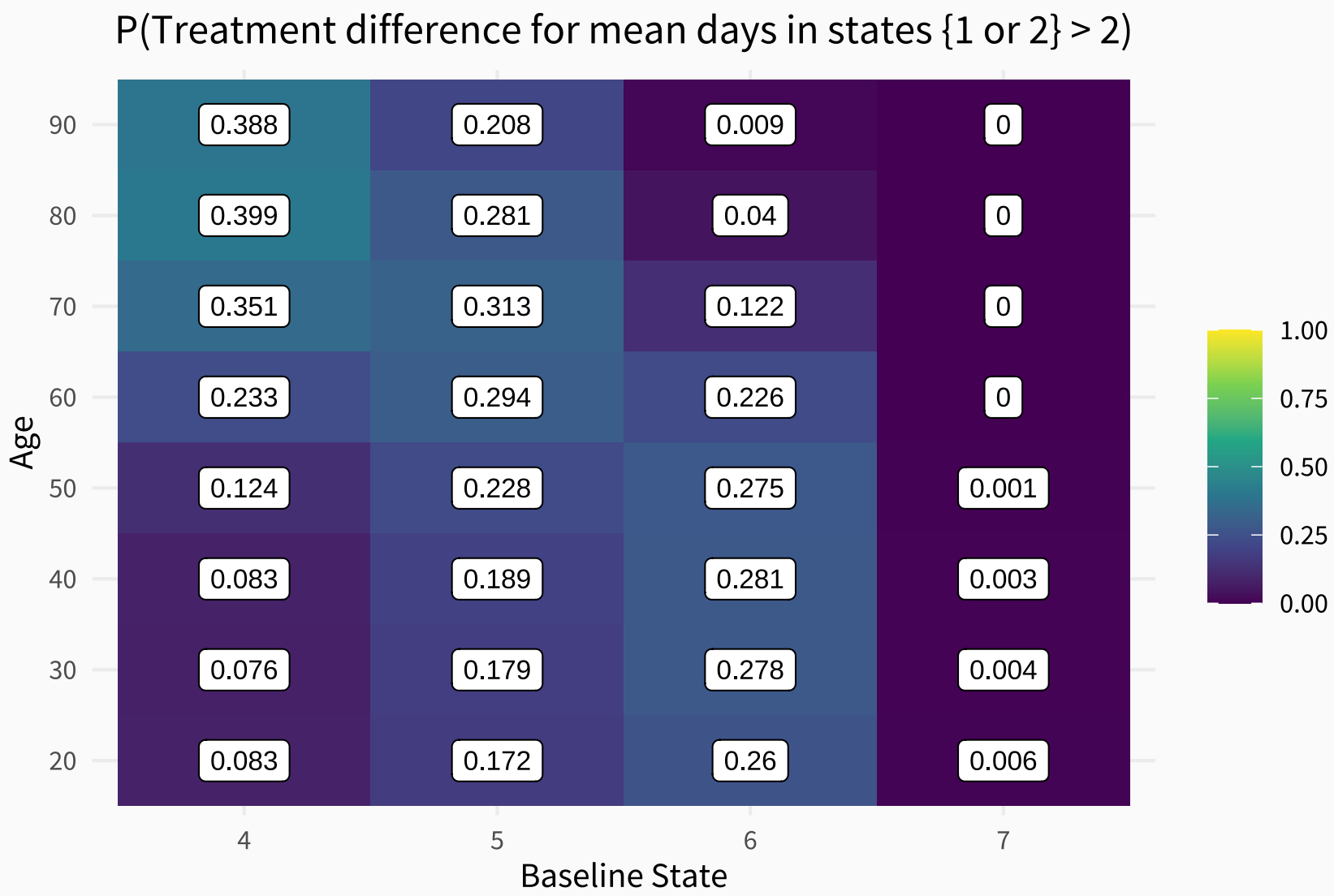


Figure 13: Probability that treatment difference is greater than 2 days at home for various covariates.

Probability of benefit (heatmap) - perturbed data

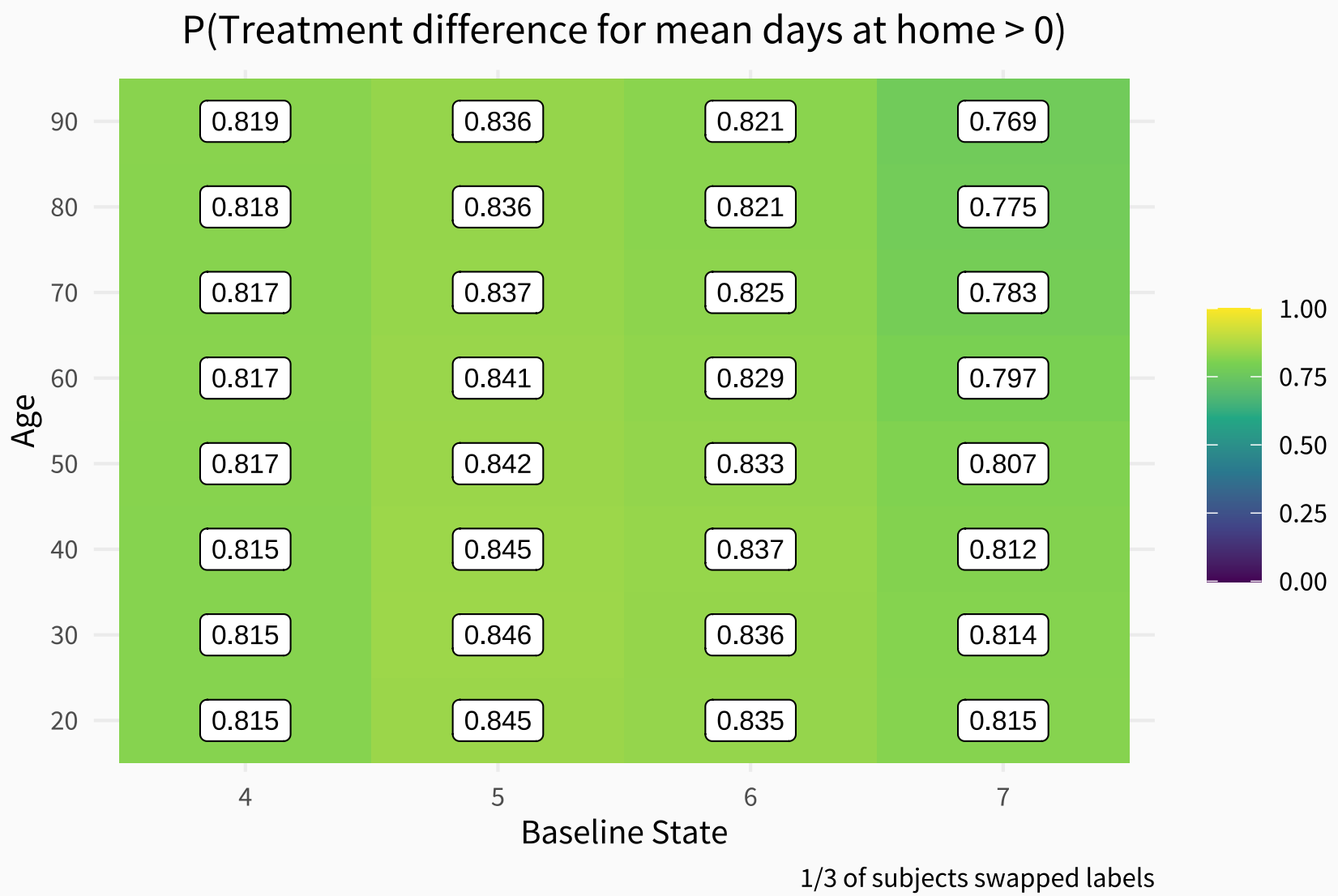


Figure 14: Probability that treatment difference is greater than 0 days at home for various covariates.

Probability of benefit (heatmap) - perturbed data

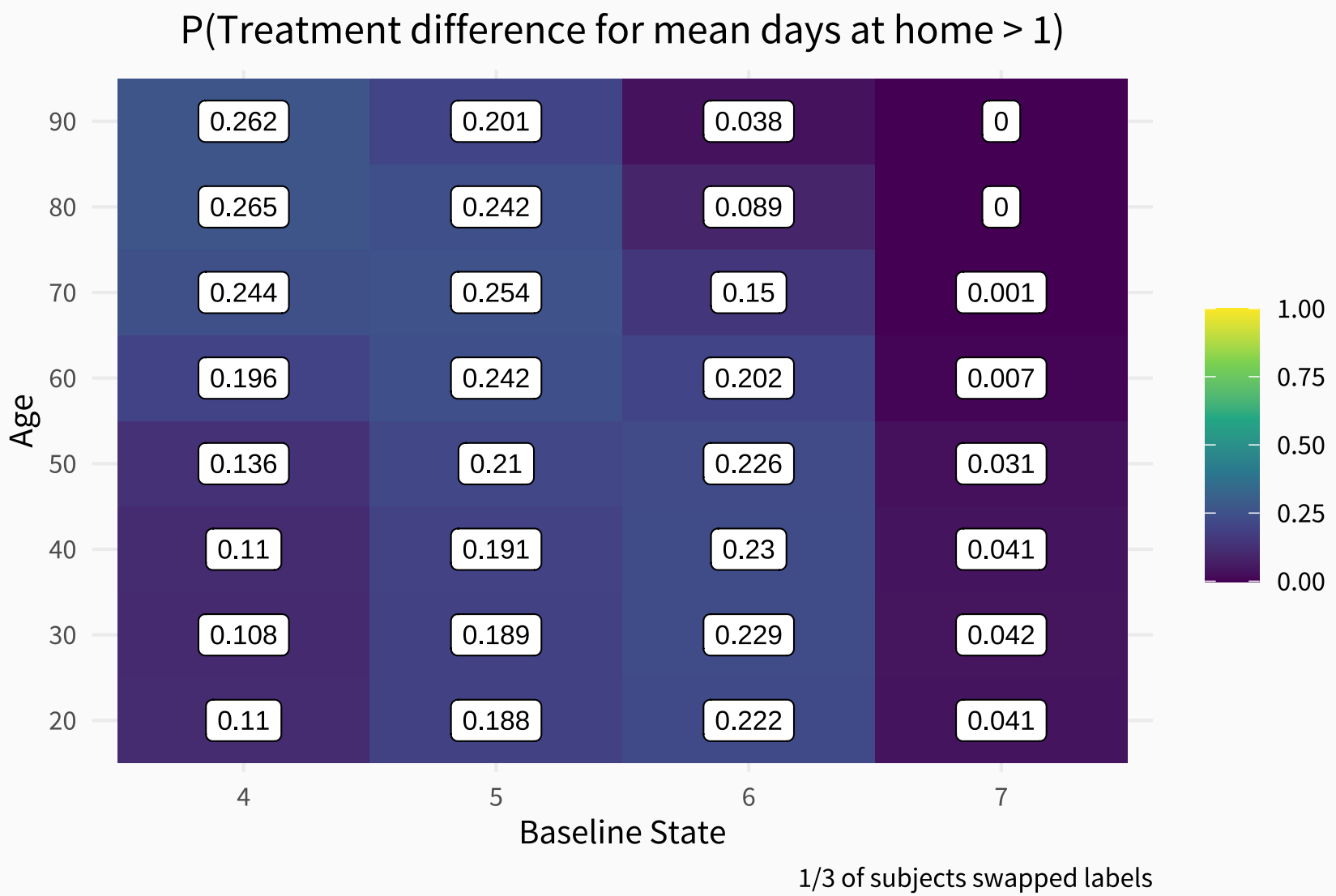


Figure 15: Probability that treatment difference is greater than 1 day at home for various covariates.

Probability of benefit (heatmap) - perturbed data

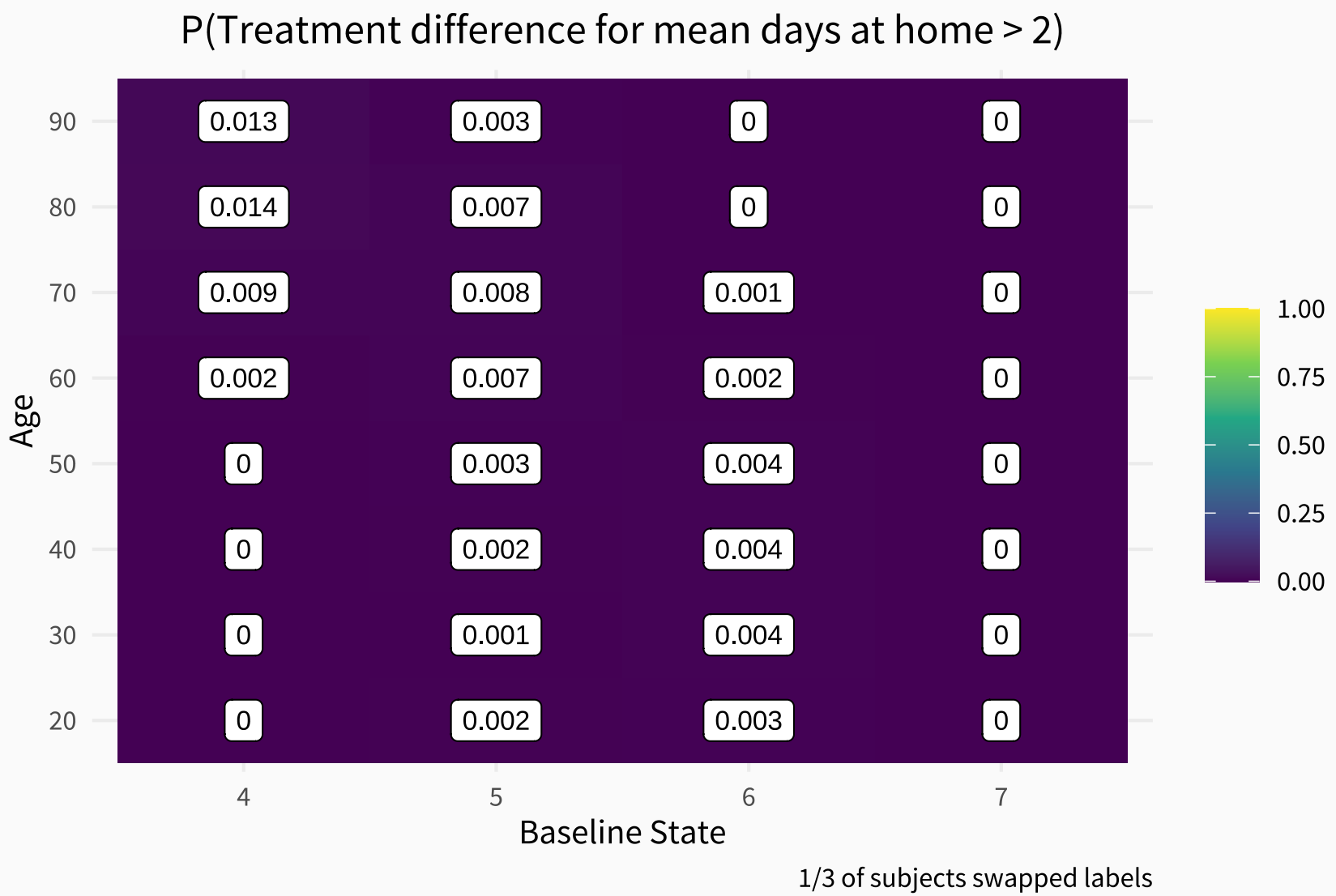
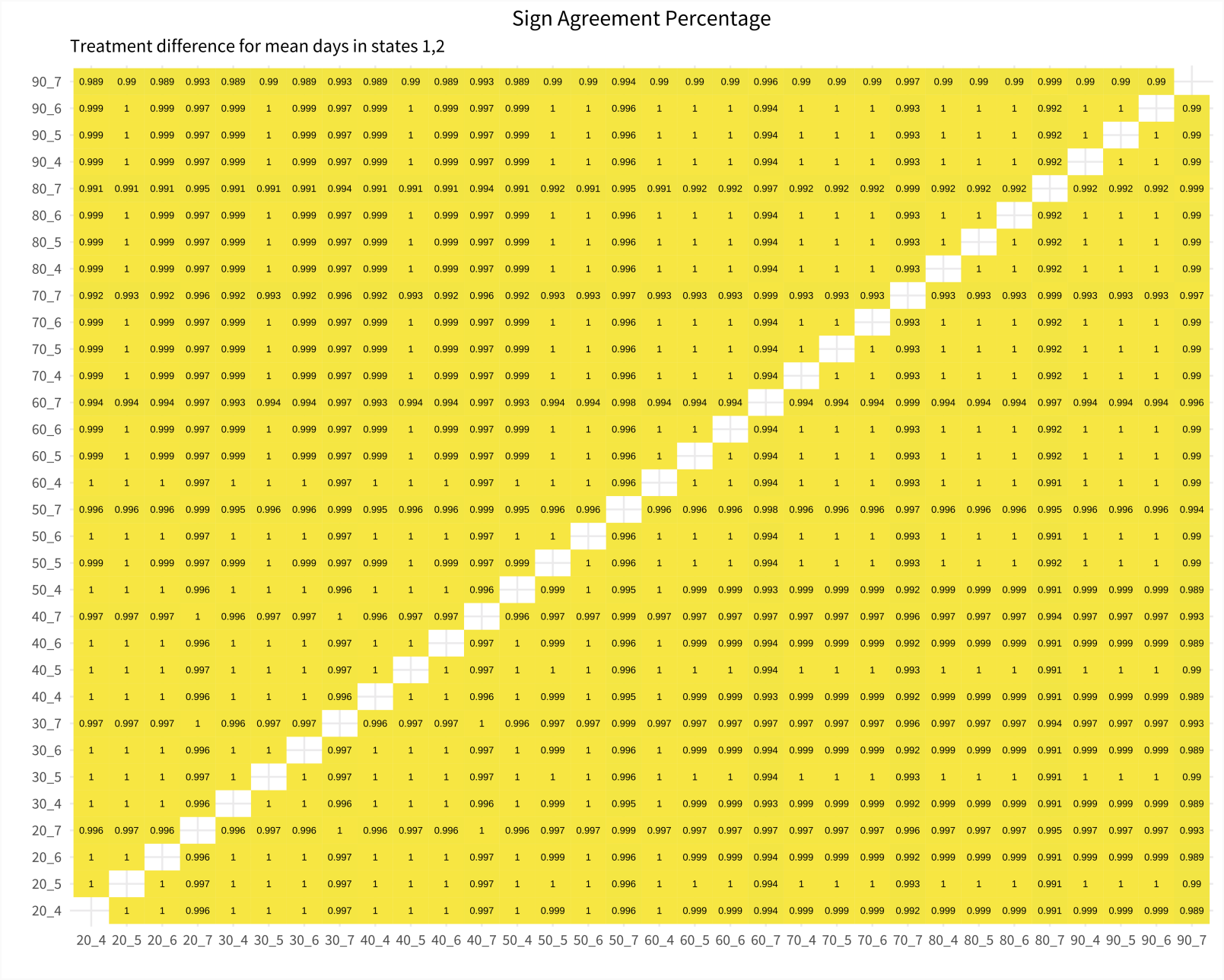


Figure 16: Probability that treatment difference is greater than 2 days at home for various covariates.

Treatment effect for days at home given different covariates are correlated

Treatment effect for days at home given different covariates agree in sign



Contrasts vs difference in mean number of days at home

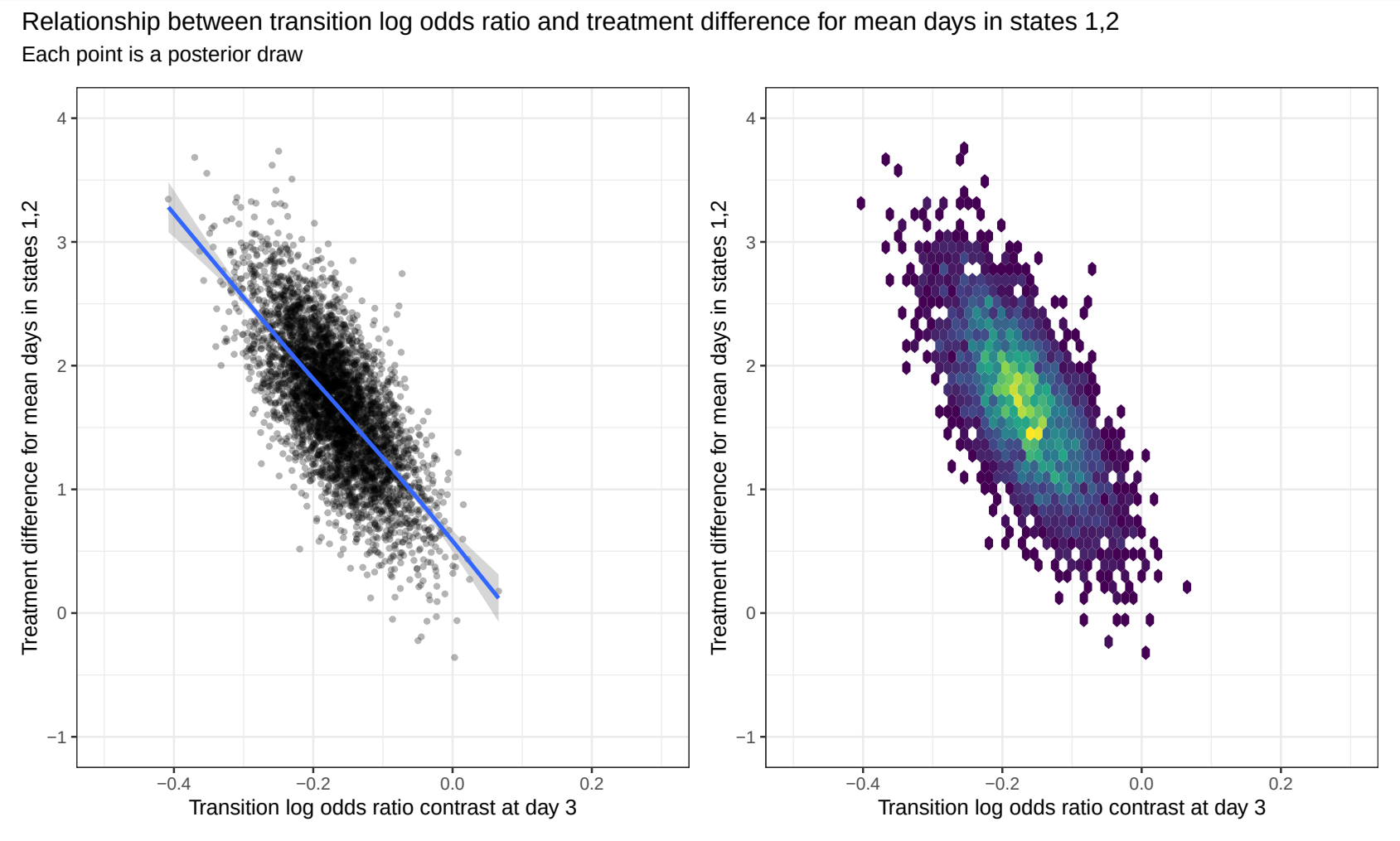


Figure 17: Remdesivir - Placebo contrast for transition log odds ratio at day 3 vs treatment difference for mean number of days at home.

Contrasts vs difference in mean number of days at home

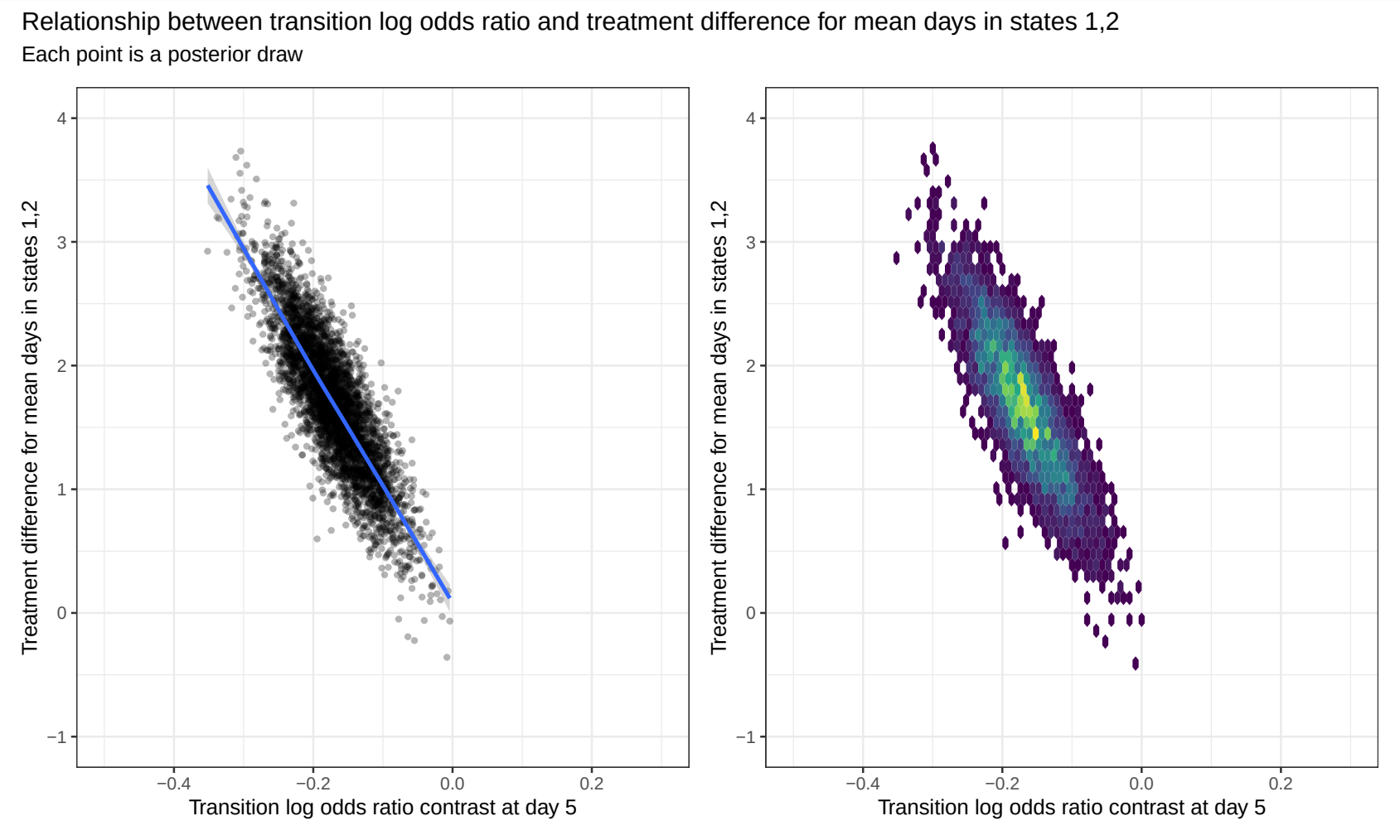


Figure 18: Remdesivir - Placebo contrast for transition log odds ratio at day 5 vs treatment difference for mean number of days at home.

Contrasts vs difference in mean number of days at home

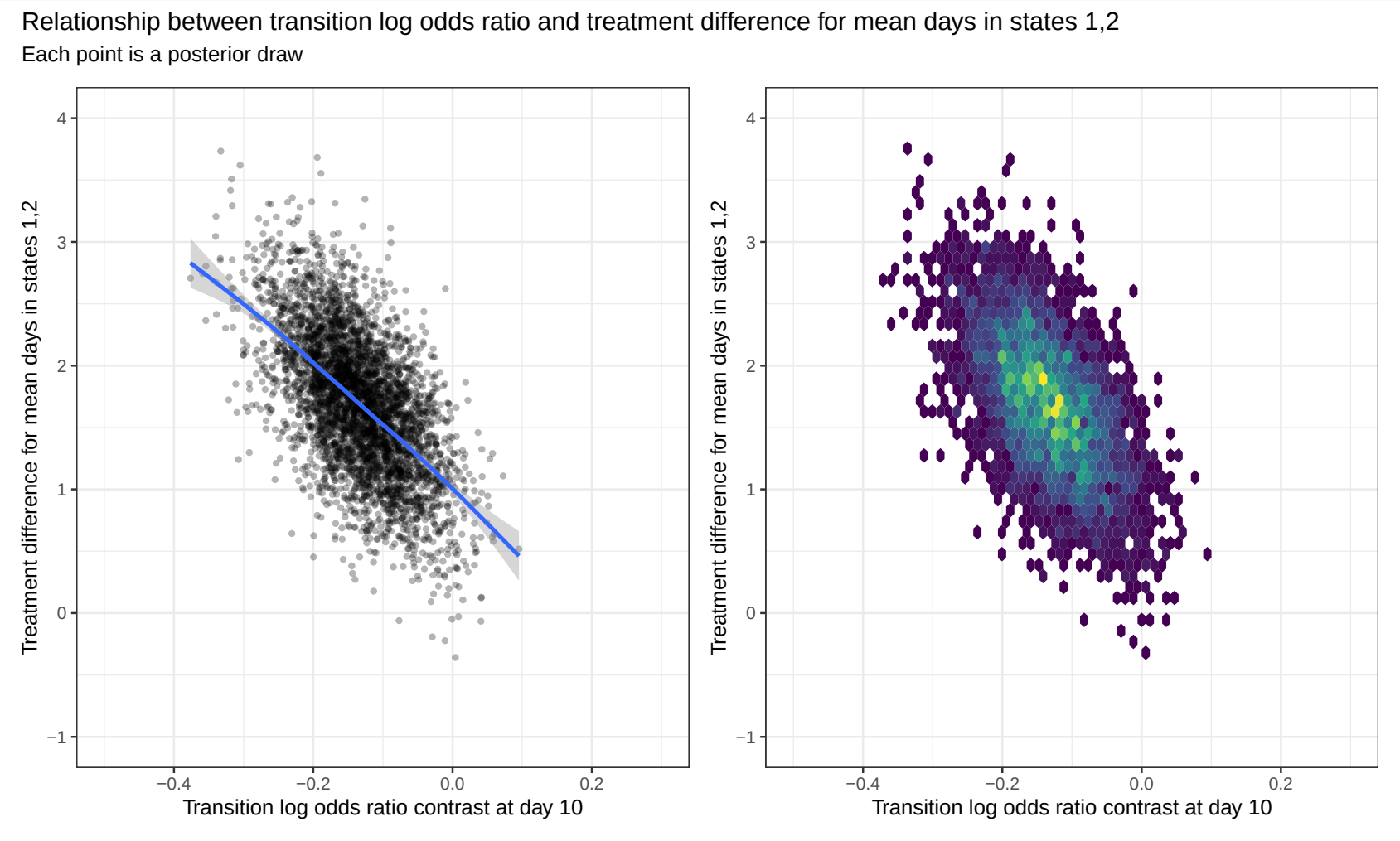


Figure 19: Remdesivir - Placebo contrast for transition log odds ratio at day 10 vs treatment difference for mean number of days at home.

Contrasts vs difference in mean number of days at home

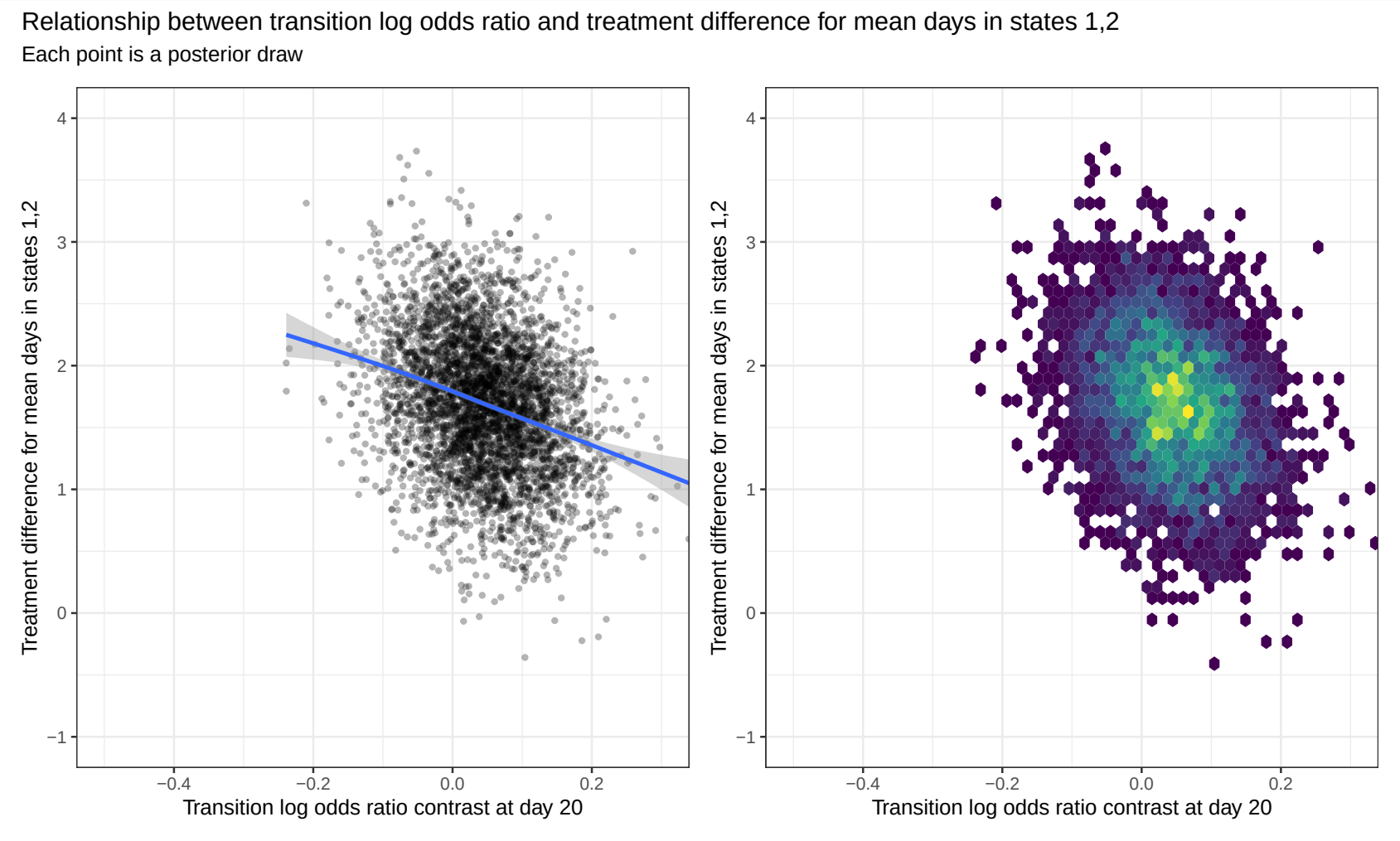


Figure 20: Remdesivir - Placebo contrast for transition log odds ratio at day 20 vs treatment difference for mean number of days at home.

Contrasts vs difference in mean number of days at home

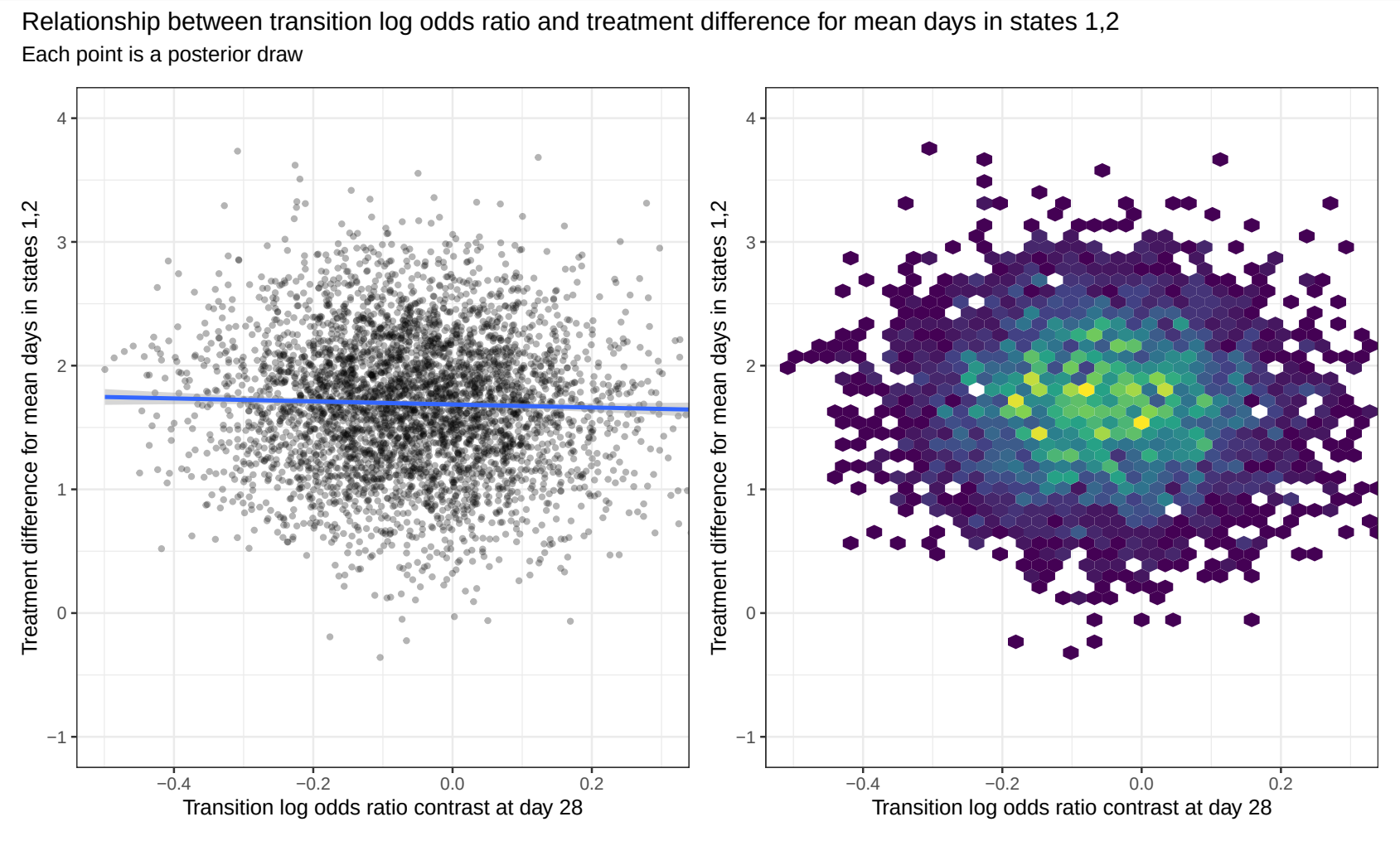


Figure 21: Remdesivir - Placebo contrast for transition log odds ratio at day 28 vs treatment difference for mean number of days at home.

Questions?