Selection of a Randomisation Procedure Does it matter? How it works!

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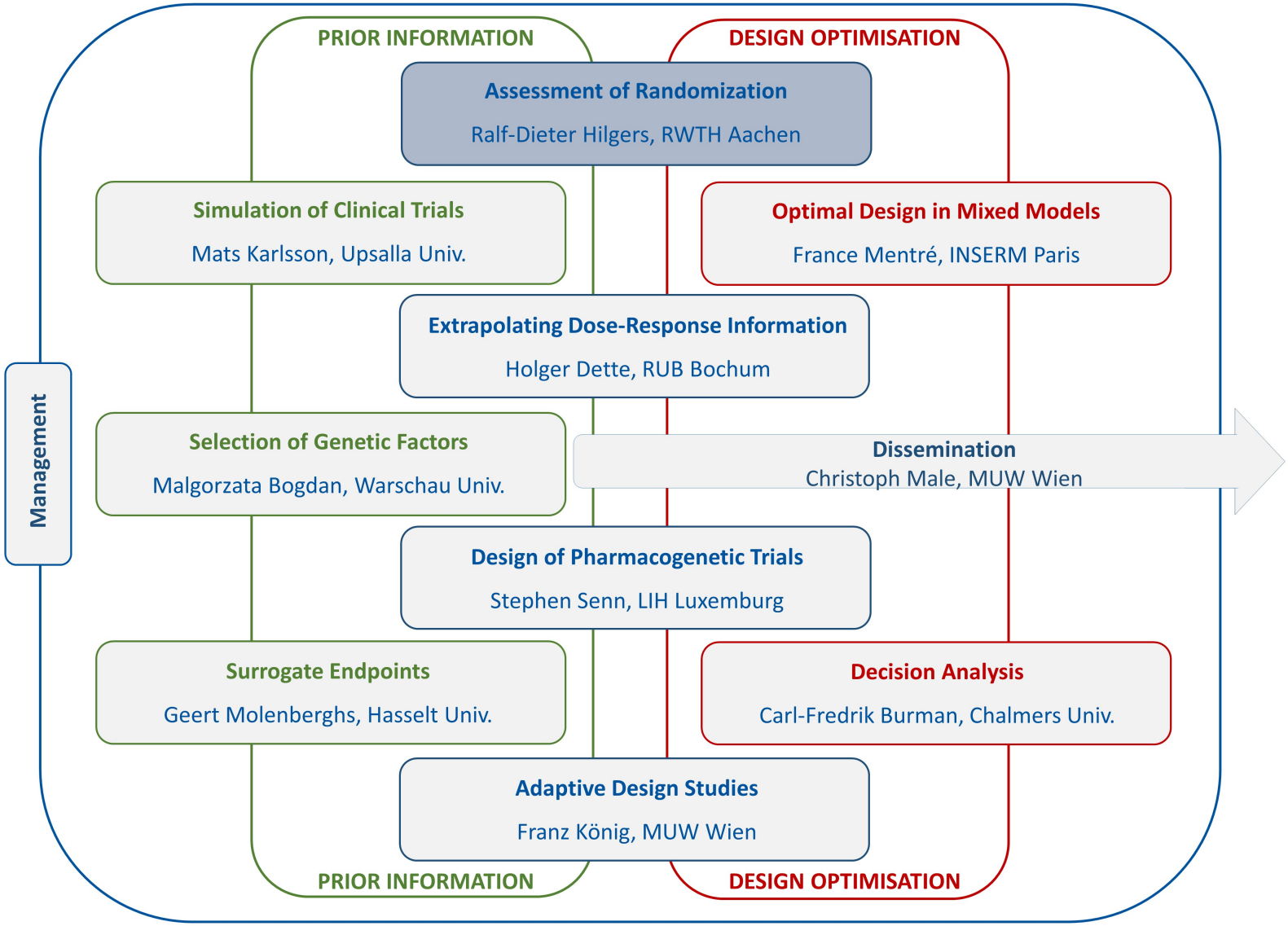
Where we are?



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What is this Webinar about?

- Randomisation is a key feature to protect against bias in randomised clinical trials.
- Does randomisation protect against bias?
- Study the impact of bias on the study results depending on the randomisation procedure.
- Show the instruments.
- Show related aspects.

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Randomisation Procedure in Practice

- ICH E9 guideline recommends to study the potential contribution of bias to the $p-$value.
- Neither the ICH guidelines nor the CONSORT statement refer to a scientific guided decision about a particular randomisation procedure and reporting standard is weak.
- The specific randomisation procedure is seldom or only partly considered in the statistical analysis.
- It seems that the selection is left to the scientists opinion.
- So why do make things complicated?

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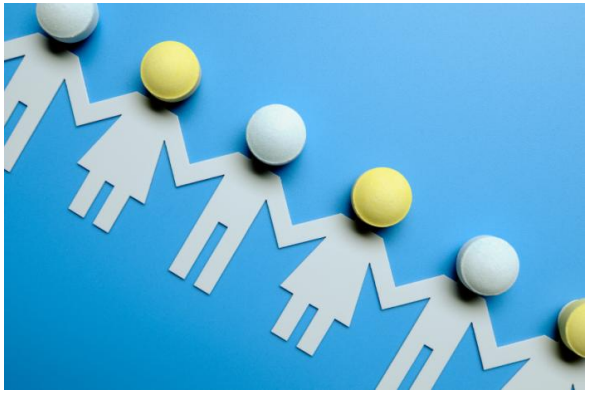
Alternating Sequence



- natural choice of treatment assignments before Bradford Hill introduces the randomisation in clinical trials *(D'Arcy Hart P. 1940)*
- still sometime favoured nowadays *(Mathe, 2005)*
- What do you think about this?

Alternating Sequence - Selection Bias - Impact on Stu Results

Can the effect of selection bias be measured?

	total sample size N				
	12	24	48	96	192
Effect size (efs)	1.796	1.197	0.826	0.578	0.408
$\frac{efs}{4}$	0.45	0.30	0.21	0.14	0.10
α	0.10867	0.10799	0.10783	0.10787	0.10827

Alternative Procedures (I)

- Ok, “tossing coin” randomisation or more precisely use complete randomisation.

Balancing of sample size ?

Alternative Procedures (II)

- Ok, keep the number of allocations to the treatment groups fixed or more precisely use random allocation rule.
- Ok, let's do block randomisation, or more precisely use permuted block randomisation.

Balancing of sample size important?

Table: Balancing behaviour and Power, t-test at twosided 5% significance level

	total sample size N				
	12	24	48	96	192
Ratio $\frac{n_1}{n_2}$	2:1	2:1	2:1	2:1	2:1
Power	75%	75%	75%	75%	75%

Does Randomisation Do a Good Job?

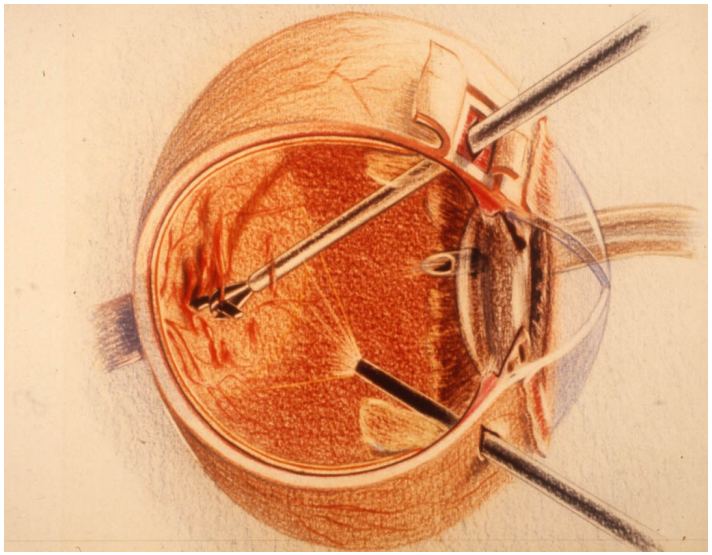
SPR-Study: Multicenter, randomised (open label), prospective clinical trial comparing scleral buckling (SB) versus primary vitrectomy (PPV) in rhegmatogenous retinal detachment of medium complexity, change in BCVA

Surgeon no 12 (n = 36)

- SB $-1.046(0.711)$, PPV $-0.390(0.662)$
  Welch t-test: $p = 0.0071$
- LR test for treatment: 5.59 ($p = 0.0179$).
- LR test for selection bias: 0.007 ($p = 0.9338$).

Surgeon no 13 (n = 34)

- SB $-0.707(0.622)$, PPV $-0.680(1.048)$
  Welch t-test: $p = 0.9278$
- LR test for treatment: 1.27 ($p = 0.2593$).
- LR test for selection bias: 3.577 ($p = 0.0586$).



(Heimann, 2007)
(Kennes, 2015)

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Study Design in Practice - Summary

- there seem to be an impact of selection bias irrespective of randomisation
- no randomisation procedure performs best with all criteria
  - Rosenberger (2016), Atkinson (2014)
- no recommendation to give scientific arguments for the choice of randomisation procedure
  - ICH Guidelines
  - CONSORT Statement

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Work program of WP2: Randomisation

- Assessment of randomisation procedures with respect to impact of bias on test results
- Development / Recommendation of adequate randomisation procedures for small population groups
- Development of randomisation test for small population groups

Summary: CSE - Randomisation

1. **Introduction** - intend select the best practice randomisation procedure (RP) to improve the level of evidence
2. **Objective** - select a RP with respect to impact on α
3. **CSE framework**
   - **Assumptions** - selection and time trend bias
   - **Options** - set of RP's
   - **Metrics** - (empirical) type I error rate
4. **Evaluation Methods** - e.g. parallel group, continuous endpoint,
5. **Software** - randomizeR
6. **Result** - report
7. **Discussion**
   - **Evaluation concept**
   - **Clinical implication** select the best practice (RP)
8. **Conclusion** choice of randomisation design

3.1 CSE - Assumptions: Statistical Model

Model for two arm parallel group design with continuous endpoint

$$Y_i = \mu_E T_i + \mu_C(1 - T_i) + \tau_i + \epsilon_i, \quad 1 \leq i \leq N_E + N_C$$

- test the hypotheses $H_0 : \mu_E = \mu_C$ vs. $H_1 : \mu_E \neq \mu_C$
- $T_i = 0$ or $T_i = 1$ if patient i is allocated to group C or E
- μ_j expected response under treatment $j = C, E$
- τ_i denotes the fixed unobserved "bias" effect
- errors ϵ_i iid $\mathcal{N}(0, \sigma^2)$

3.1 CSE - Assumptions: Joint Additive Bias Model

two arm parallel group trial with continuous endpoint

Joint Additive Bias

$$\tau_i = \underbrace{\theta \frac{i}{N_E + N_C}}_{\textit{time trend}} + \underbrace{\eta \ [\text{sign}(\ n_E(i-1) - n_C(i-1)\ )]}_{\textit{selection bias}}$$

- $n_j(i)$: assignments to treatment j after i allocations
- different shape of time trend or selection bias can be incorporated
- weighted additive or multiplicative bias model

3.2 CSE - Options: Randomisation Procedures

Options of CSE-randomisation

- **various randomisation procedures and their parameter settings**

RAR Random Allocation rule, fix total sample size N. randomise so that half the patients receive treatment 1

BSD(a) (Big Stick design) CR allow for imbalance within a limit a

. . .etc.

3.3 CSE - Metric: Type-I-Error Probability

ICH E9: The interpretation of statistical measures of uncertainty of the treatment effect and treatment comparisons should involve considerations of the potential contribution of bias to the p-value, confidence interval, or inference.

Metric of CSE randomisation

- $\rightarrow$ **empirical type-I-error rate**

study the empirical type-I-error rate or empirical test size via simulation

5. CSE - Software: randomizeR

. . . will use randomizeR, to conduct the evaluation and report the findings

current status of randomizeR

- implemented randomisation procedures: `CR`, `RAR`, `PBR`, `RPBR`, `HADA`, `MP`, `BSD`, `UD`, `TBD`, `EBC`, `GBC`, `CD`, `BBC`

$\Rightarrow$ generating / saving a randomisation sequence as `.csv` file

- implemented assessment criteria: `selBias`, `chronBias`, `corGuess`, `imbal`, `setPower`, `combineBias`

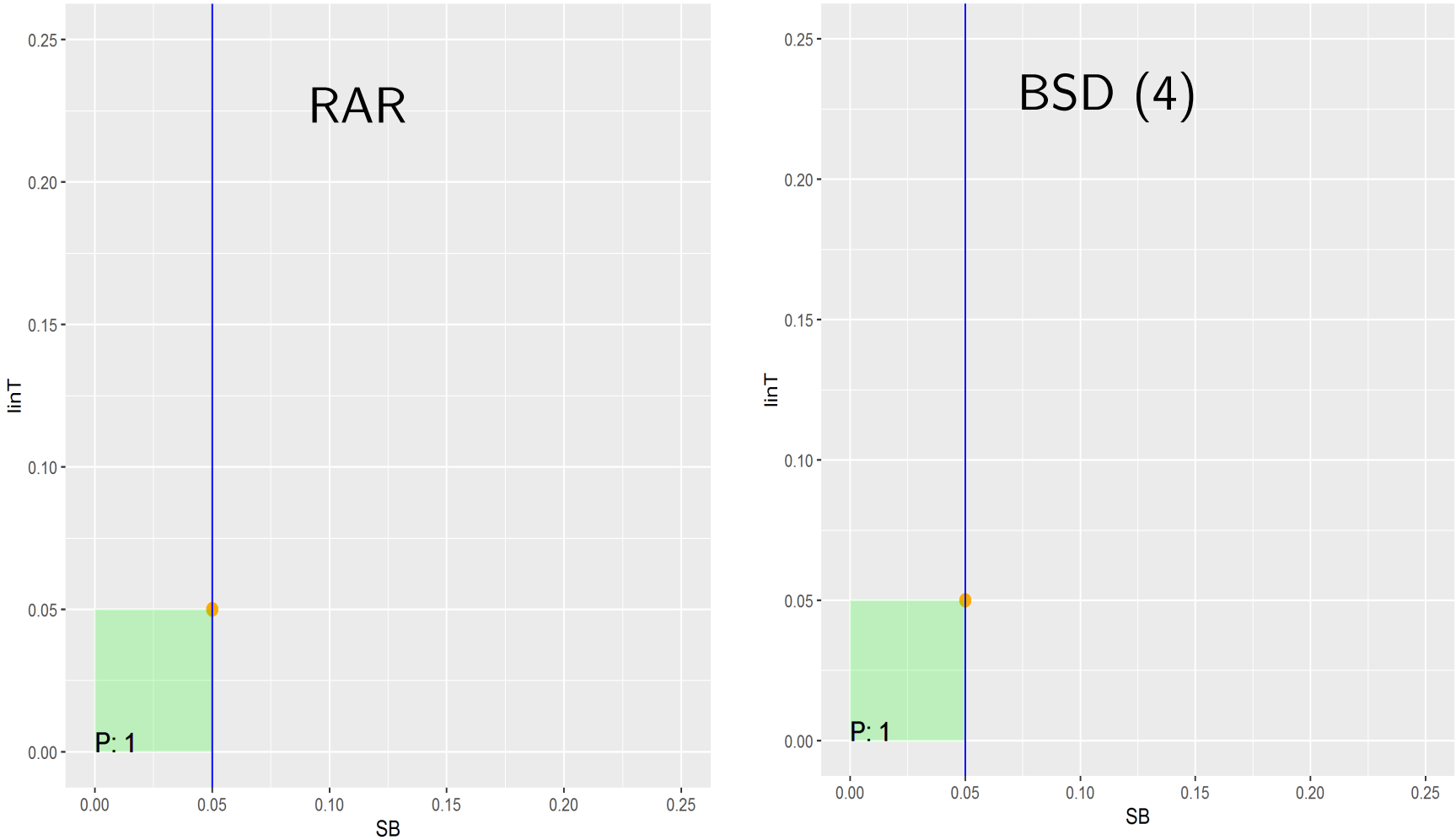
$\Rightarrow$ assessment and comparison of randomisation procedures possible

in progress\next steps

- assessment of linked criteria, randomisation tests, time to event model, multiarm model
- bias corrected test *(Uschner, 2016)*
- development of a shiny app

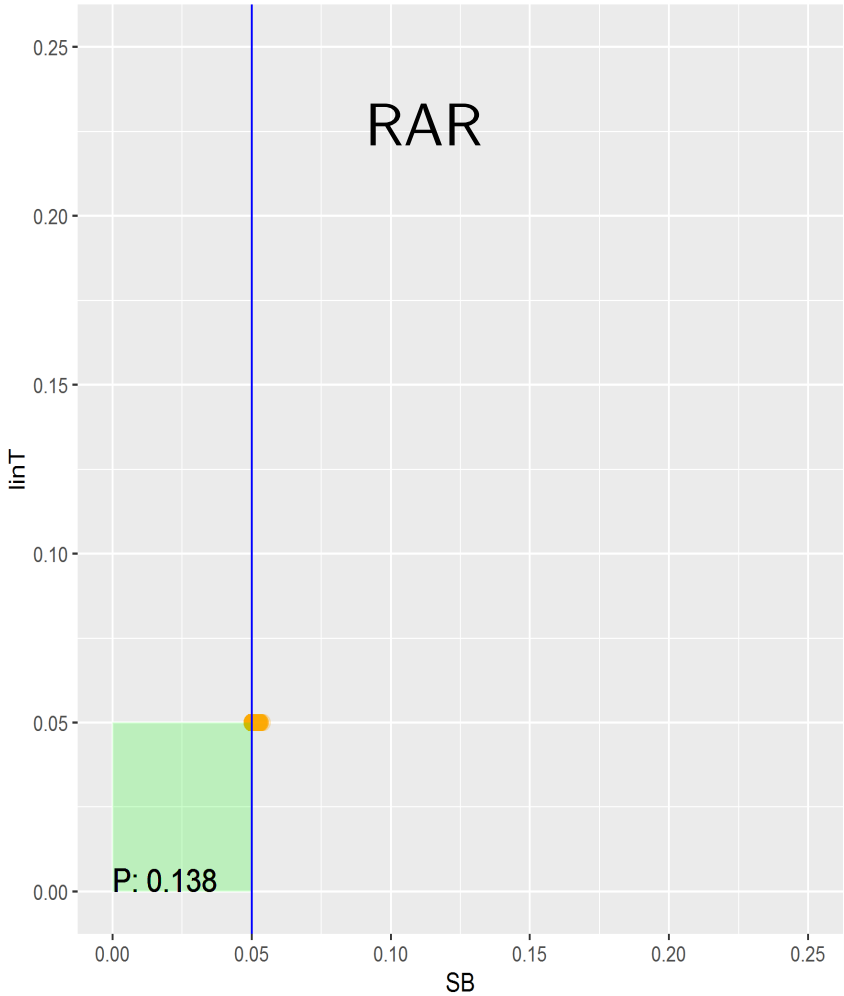
6. CSE - Result: Selection Bias (N=96)

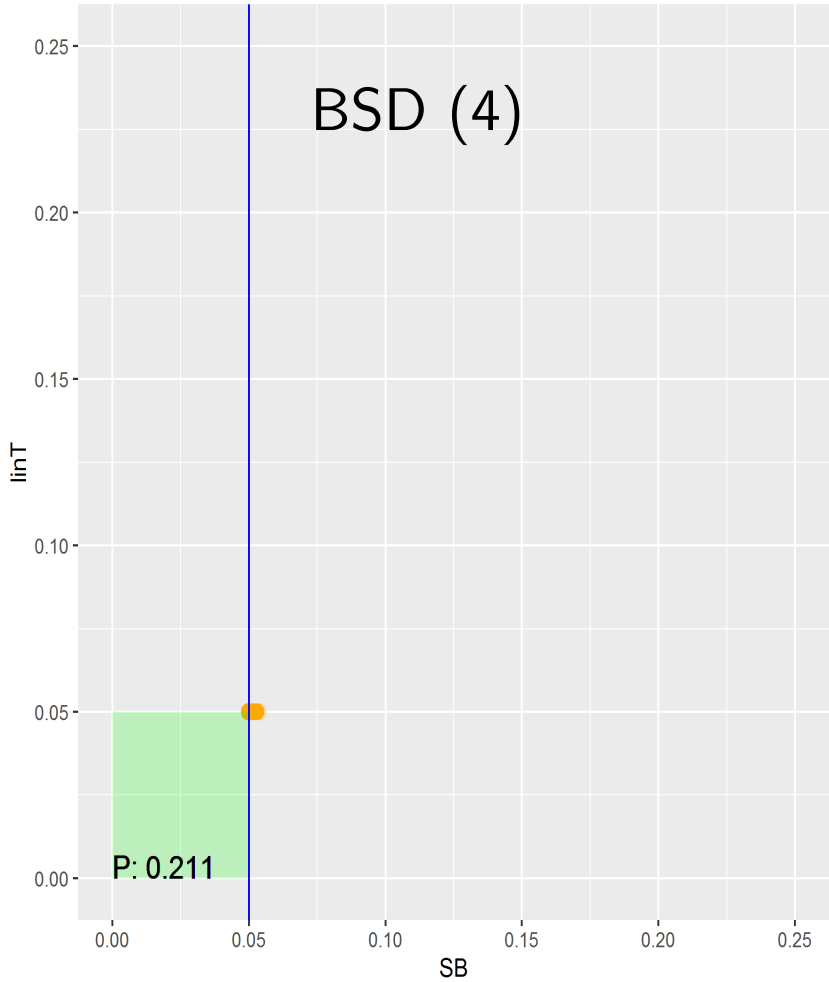
setting: $N_E = N_C = 48, \eta = 0.0 \times \delta; \theta = 0$



6. CSE - Result: Selection Bias (N=96)

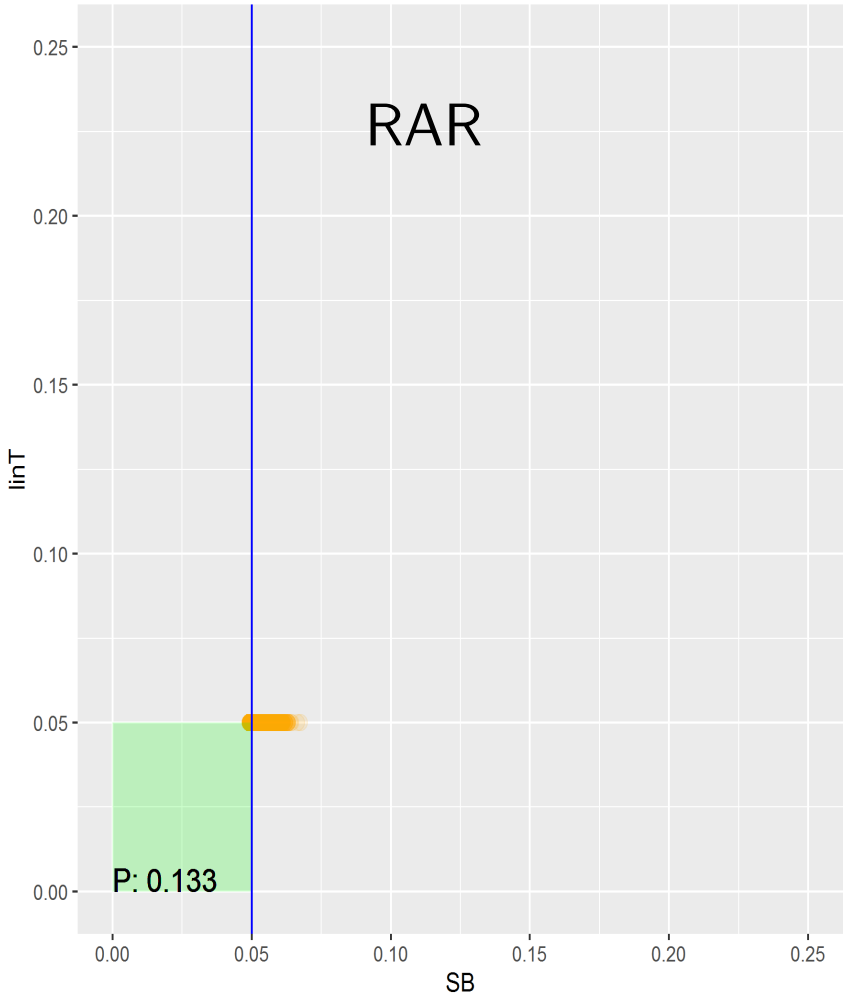
setting: $N_E = N_C = 48, \eta = 0.1 \times \delta;\ \theta = 0$

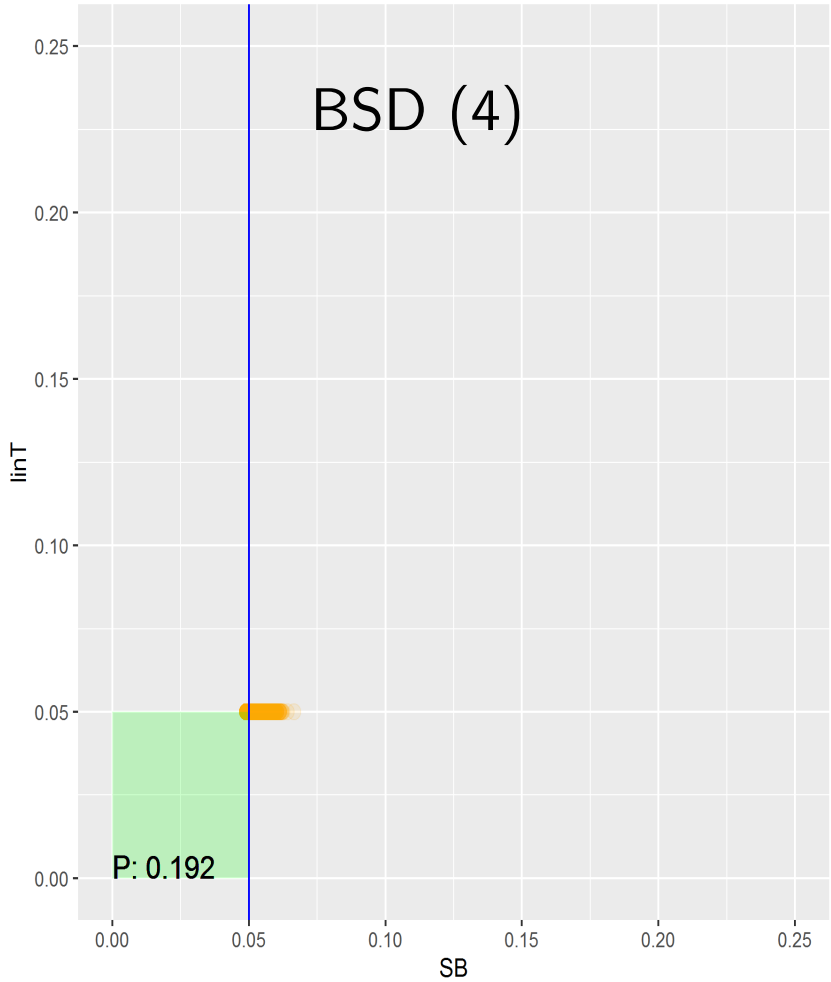




6. CSE - Result: Selection Bias (N=96)

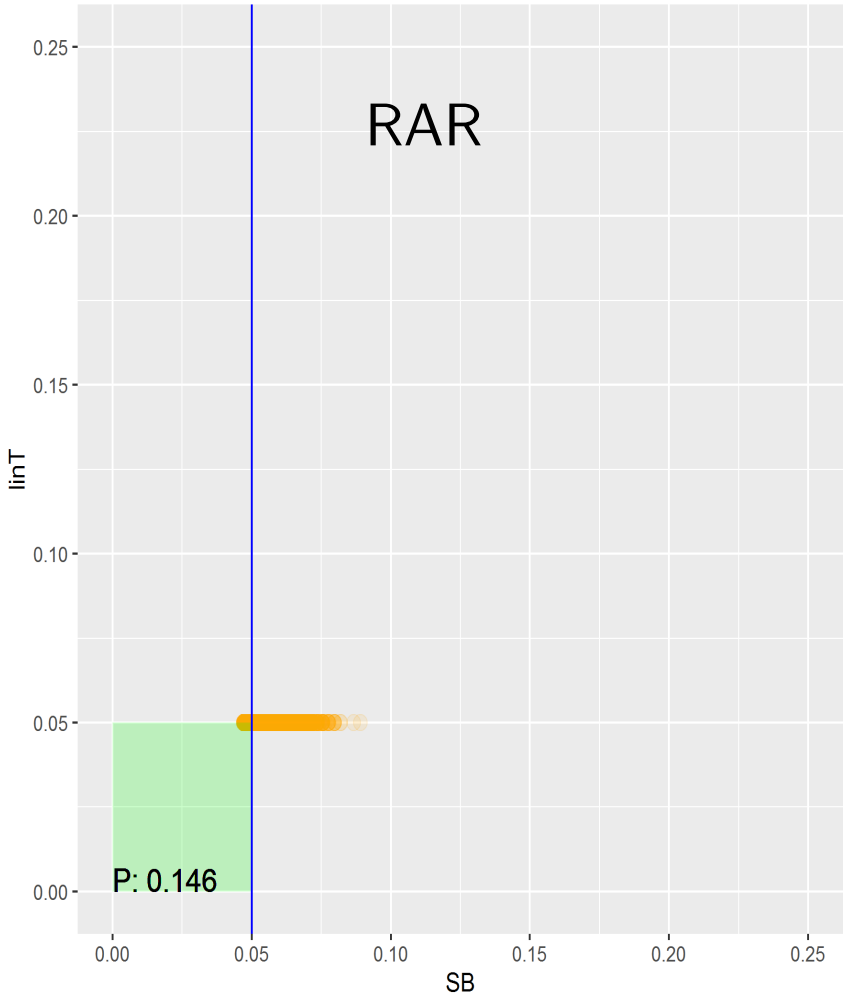
setting: $N_E = N_C = 48, \eta = 0.2 \times \delta;\ \theta = 0$

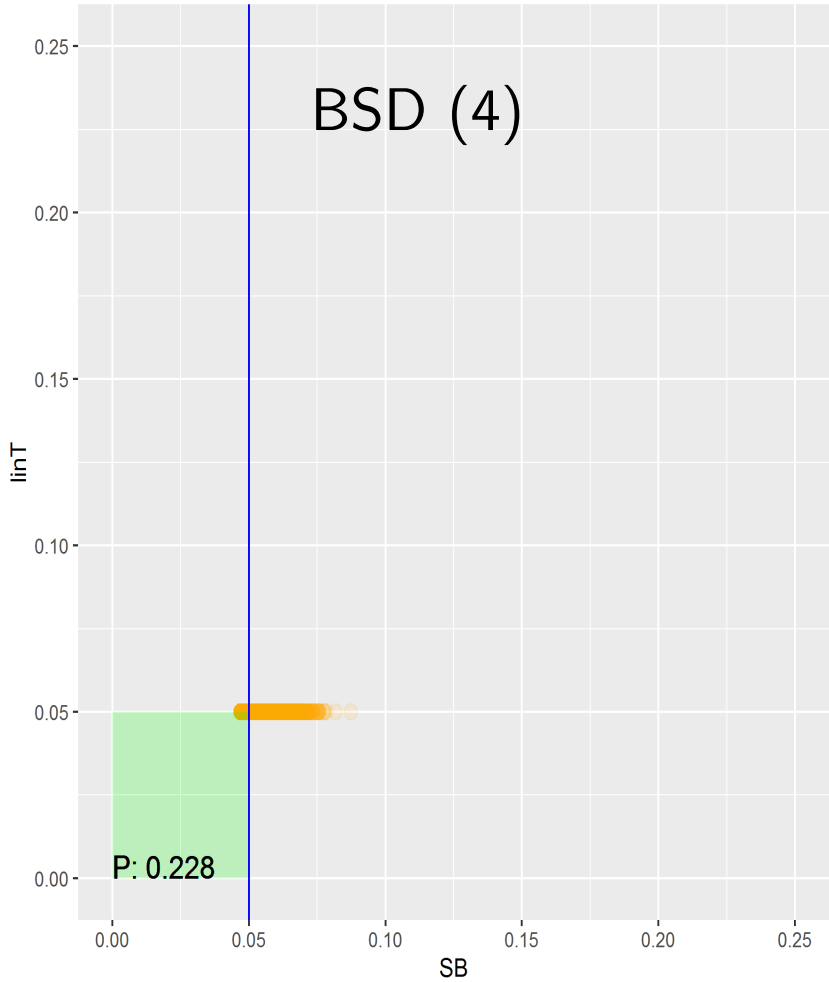




6. CSE - Result: Selection Bias (N=96)

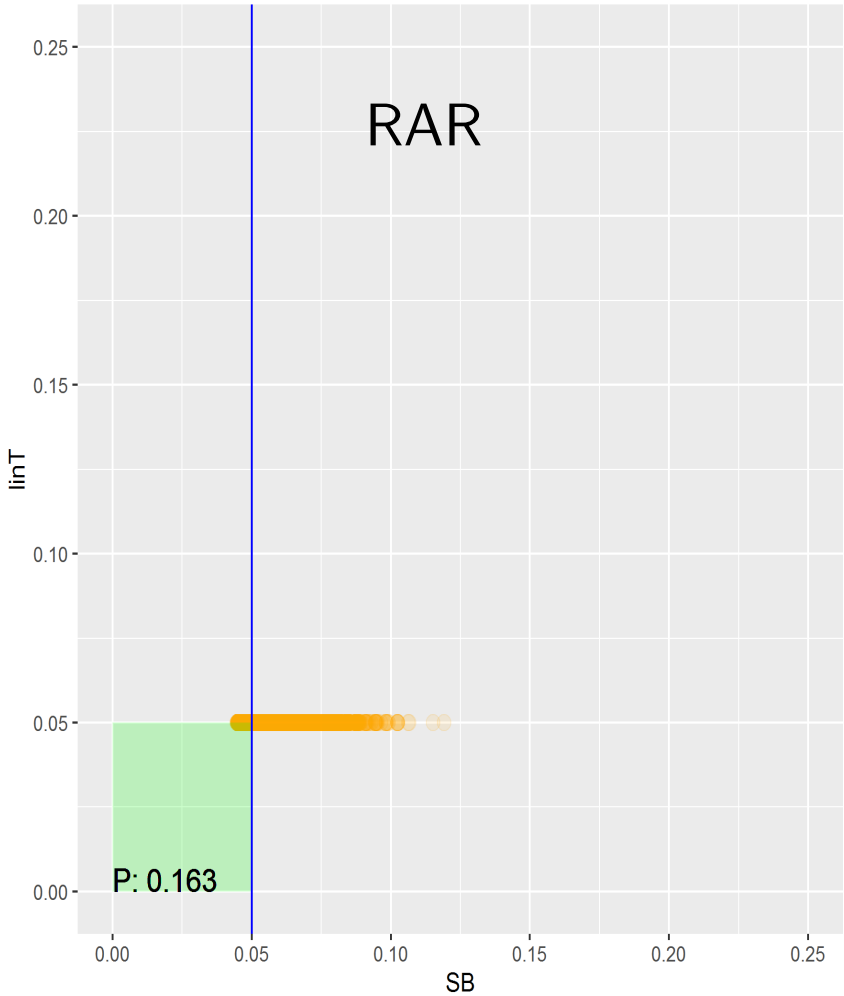
setting: $N_E = N_C = 48, \eta = 0.3 \times \delta;\ \theta = 0$

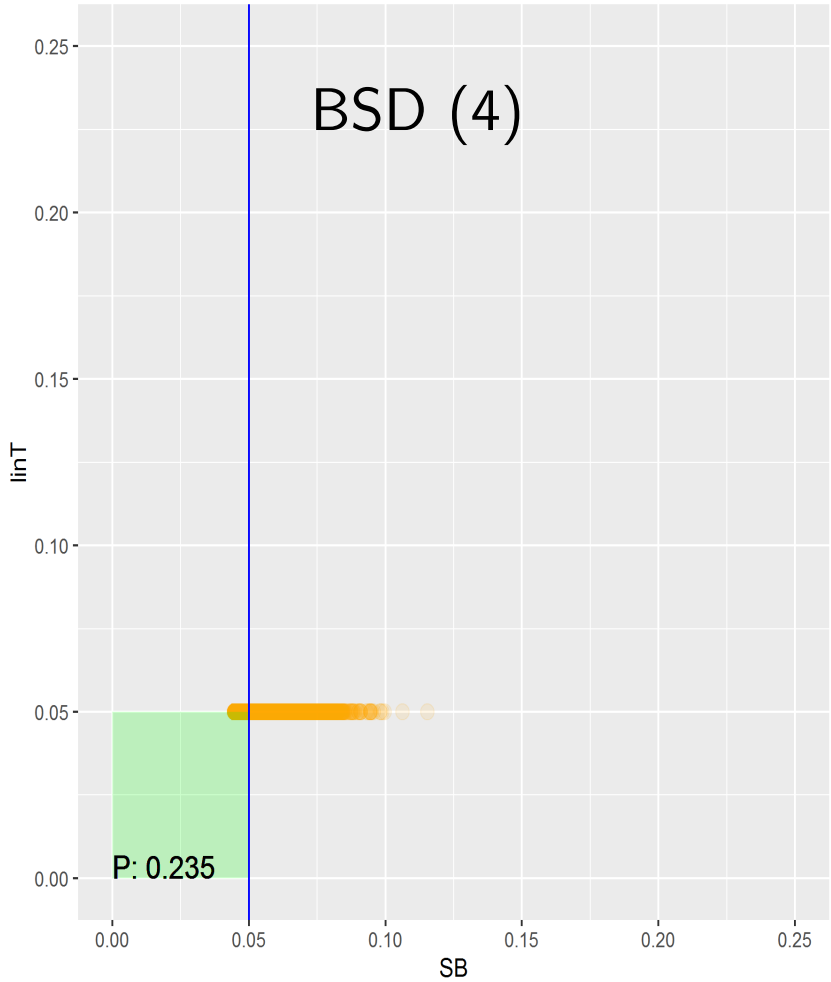




6. CSE - Result: Selection Bias (N=96)

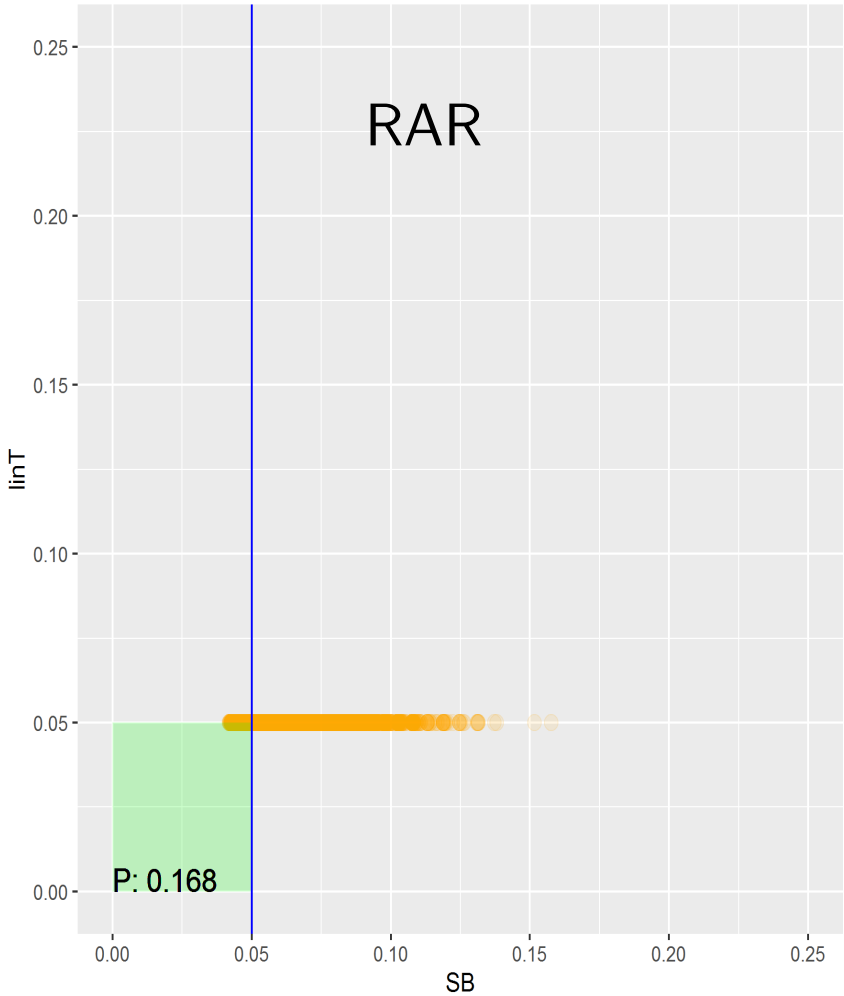
setting: $N_E = N_C = 48, \eta = 0.4 \times \delta; \theta = 0$

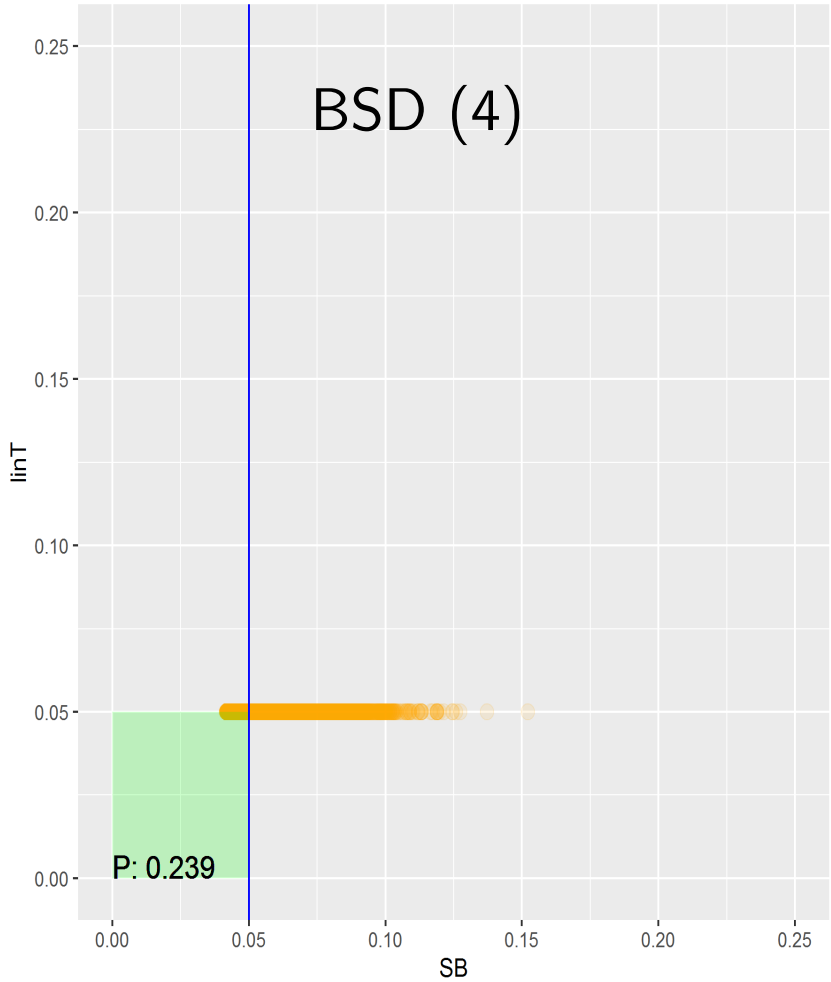




6. CSE - Result: Selection Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0.5 \times \delta; \theta = 0$





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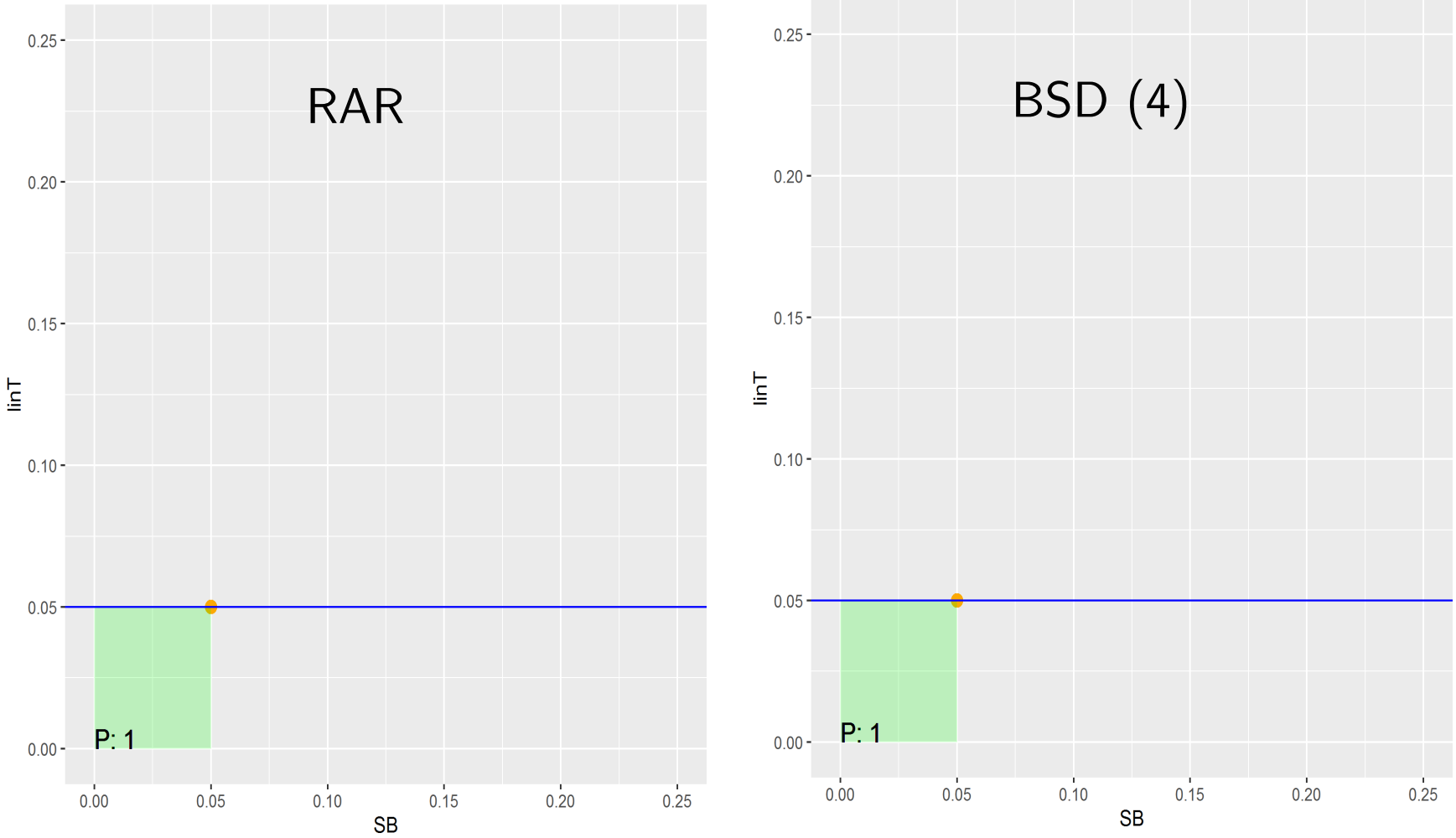
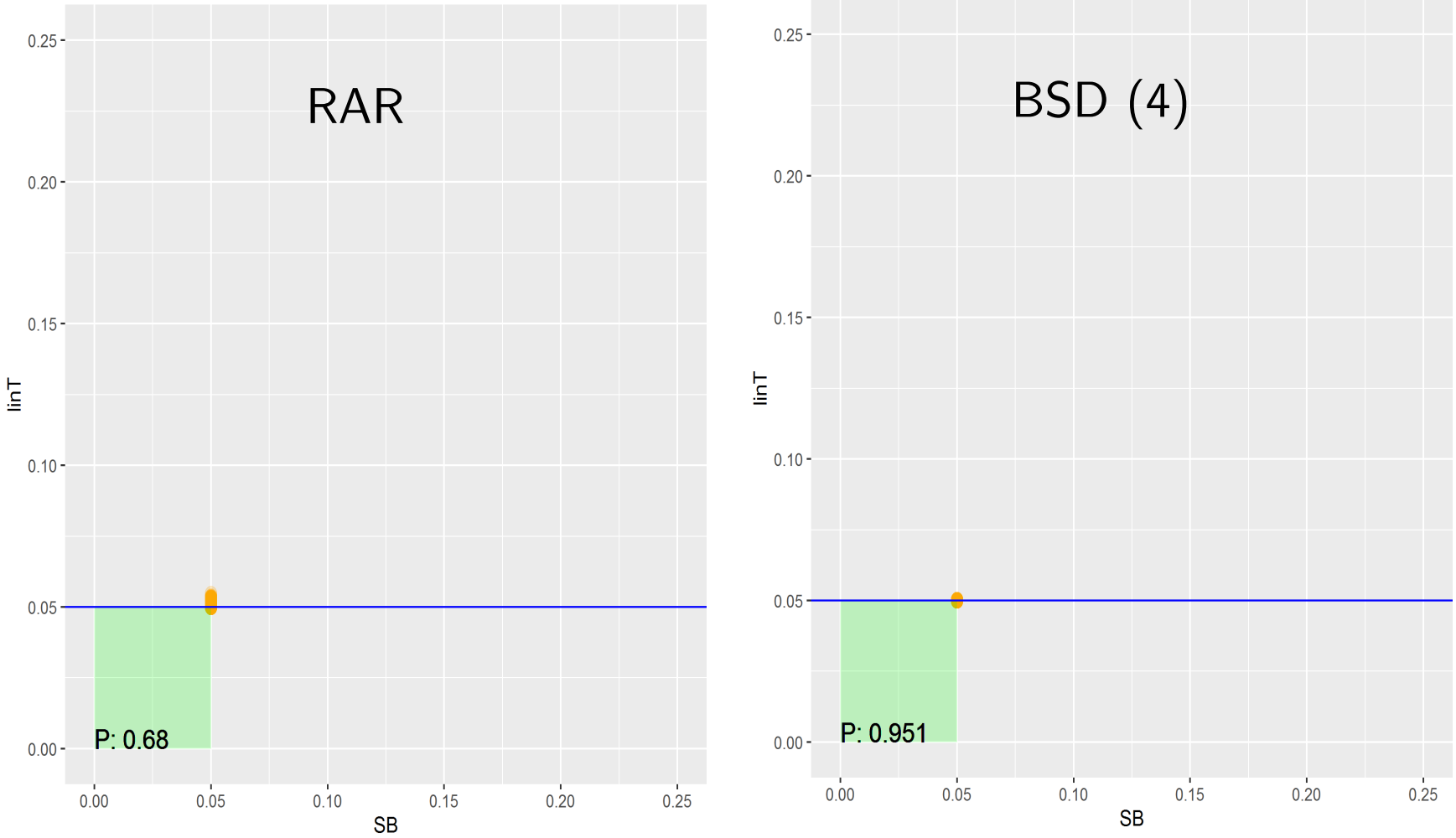
6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 0.0 \times \sigma$



6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 0.2 \times \sigma$



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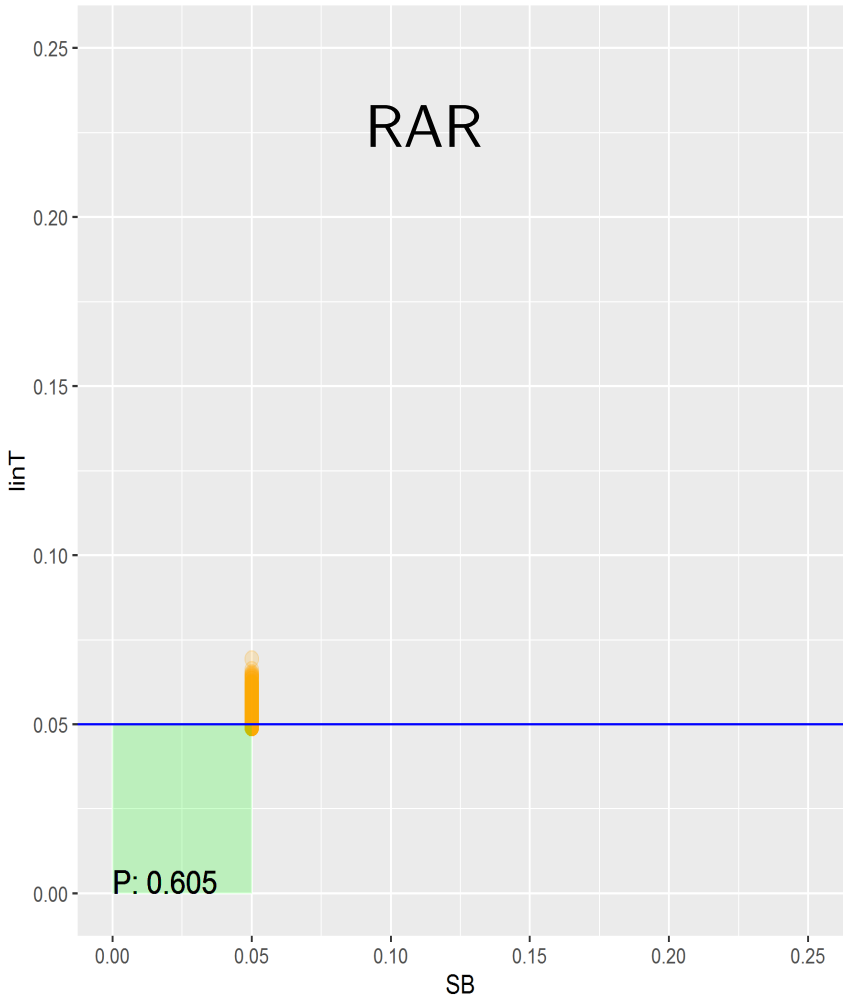
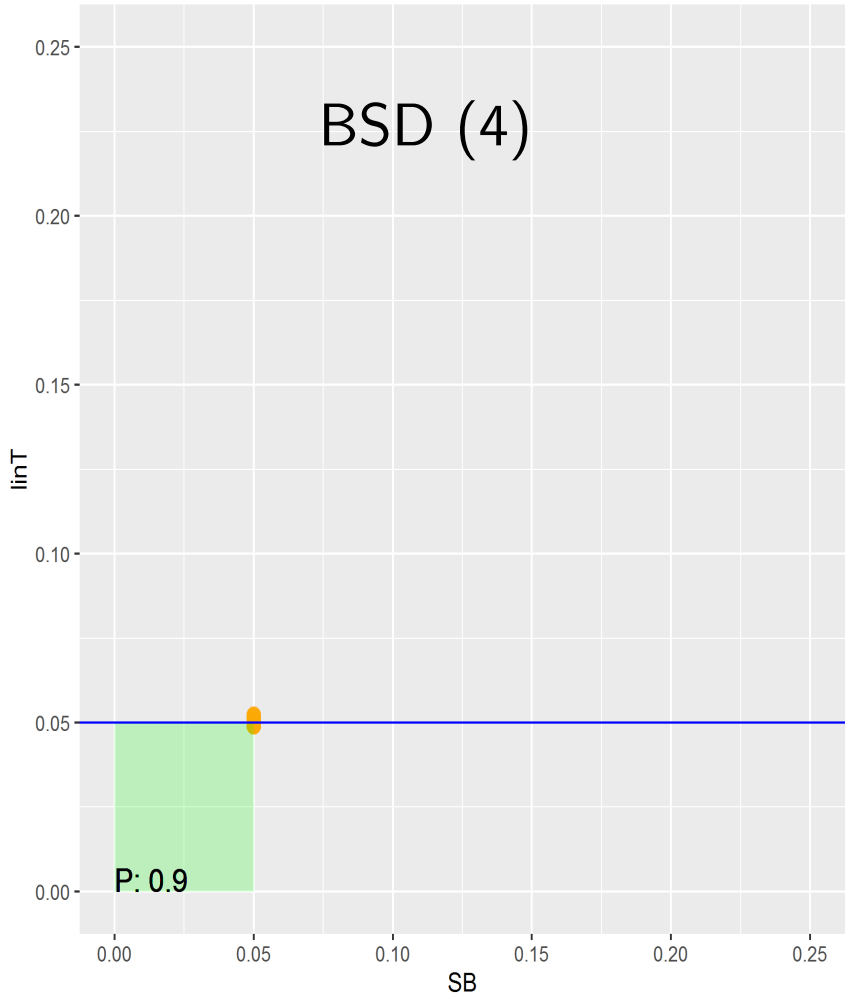
6. CSE - Result: Linear Time Trend Bias (N=96)

setting: $N_E = N_C = 48, \eta = 0; \theta = 0.4 \times \sigma$





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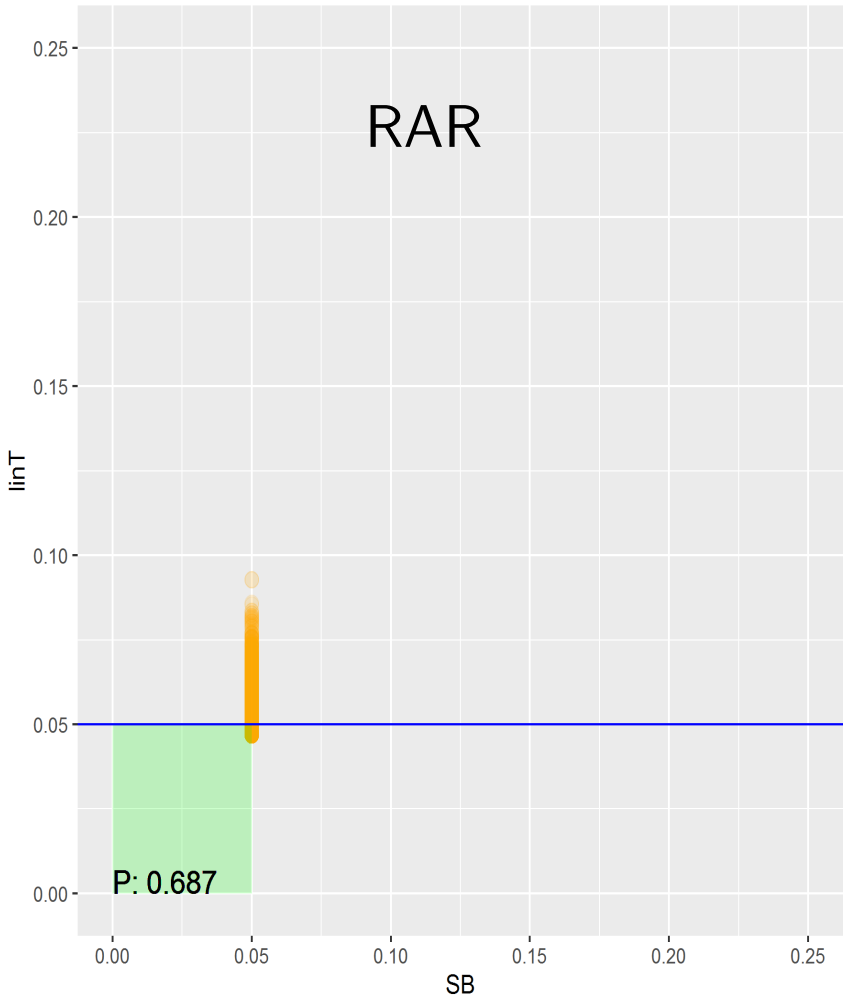
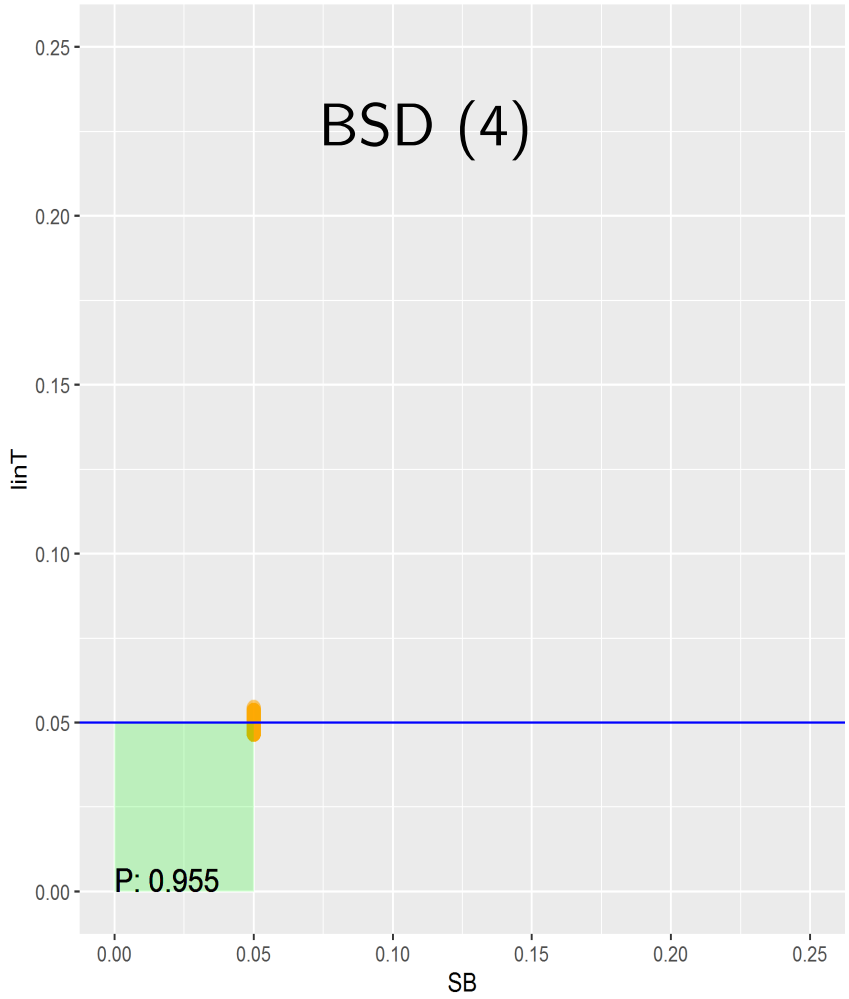
6. CSE - Result: Linear Time Trend Bias (N=96)

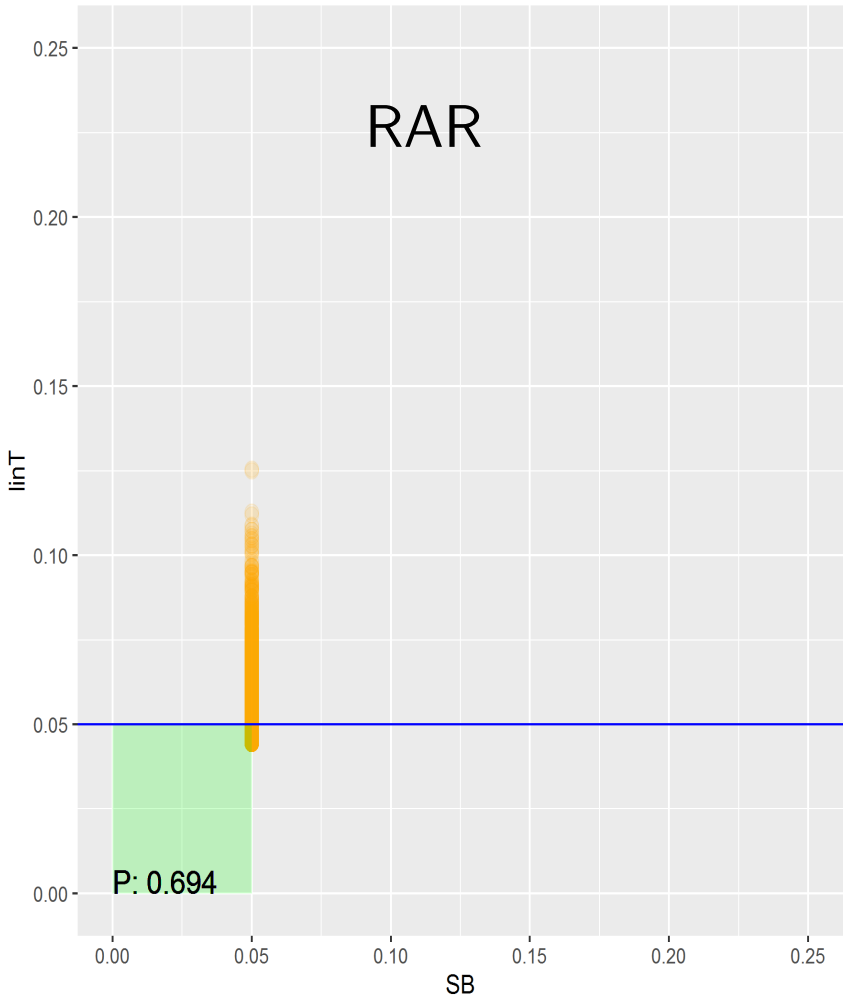
setting: $N_E = N_C = 48, \eta = 0; \theta = 0.6 \times \sigma$

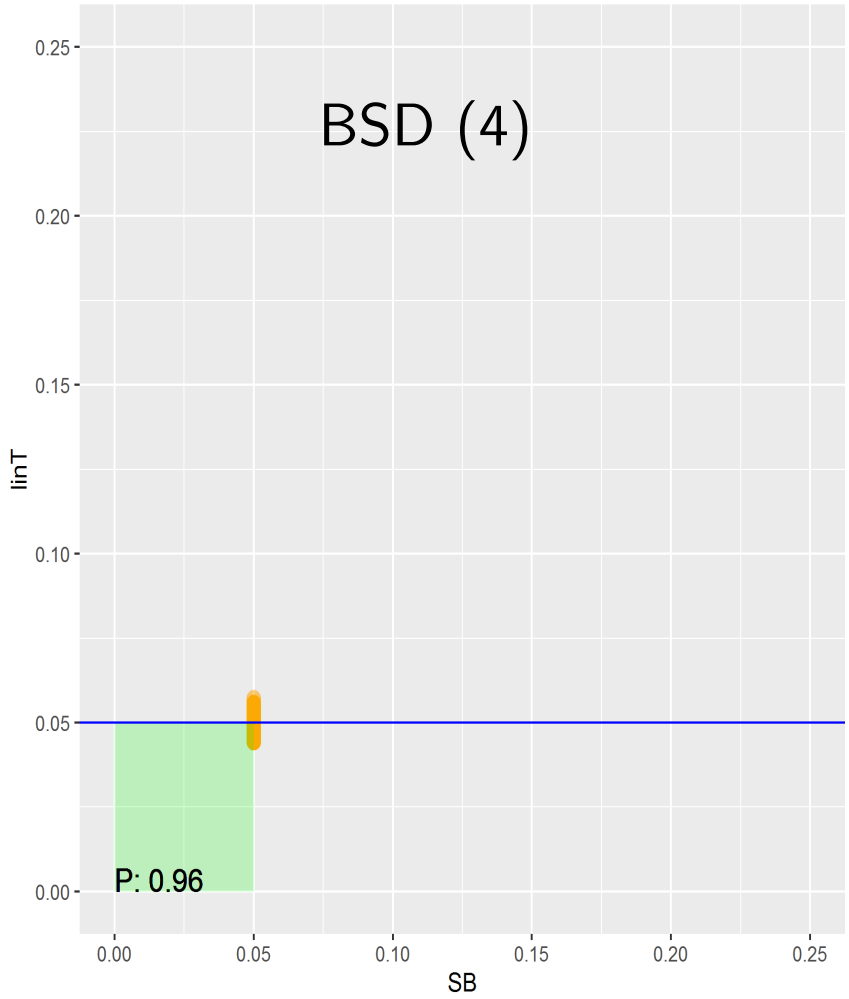




6. CSE - Result: Linear Time Trend Bias (N=96)

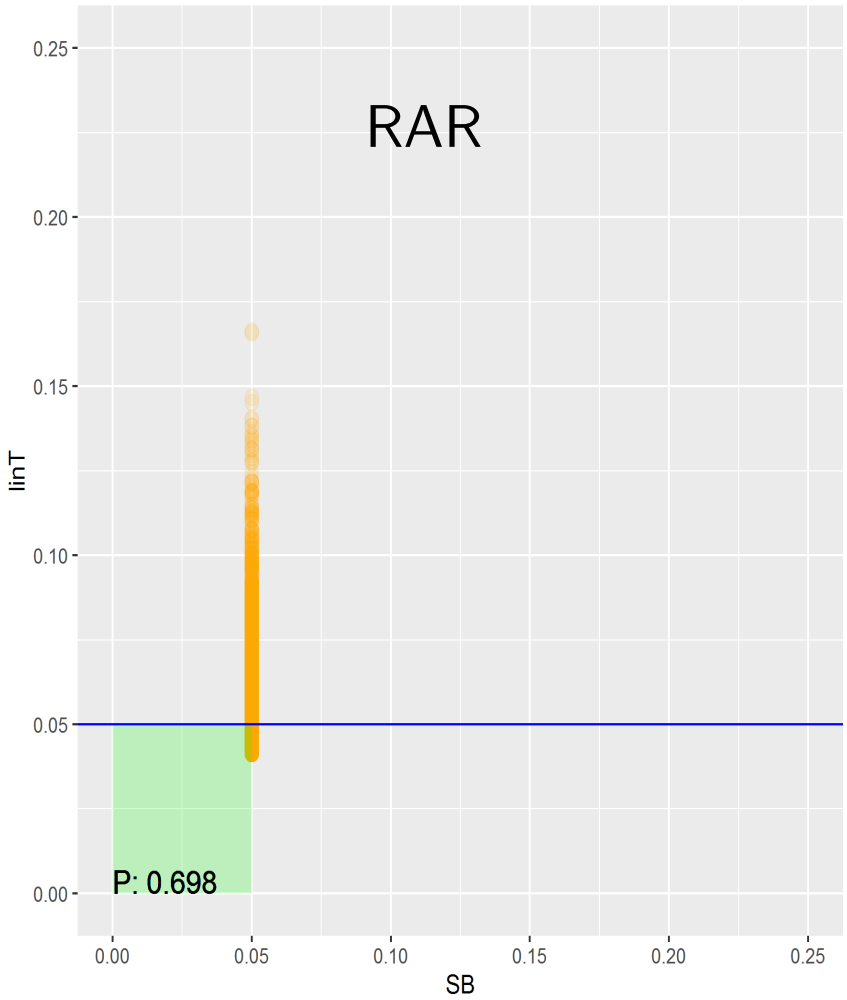
setting: $N_E = N_C = 48, \eta = 0; \theta = 0.8 \times \sigma$

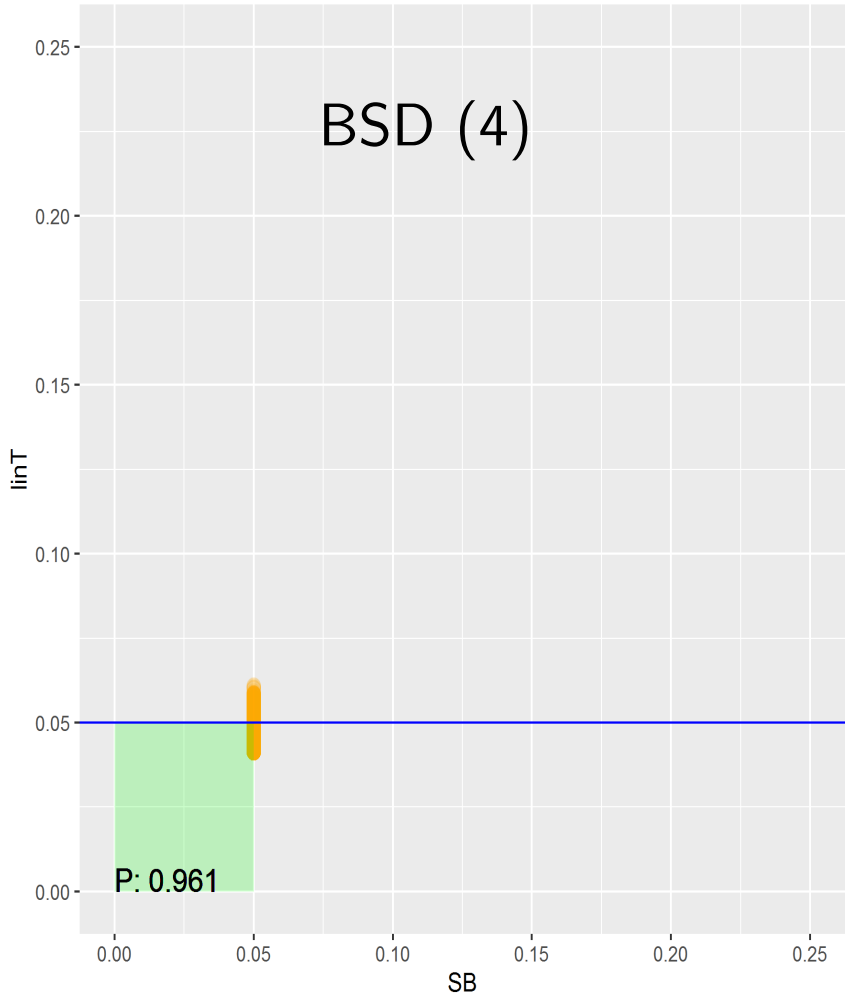




6. CSE - Result: Linear Time Trend Bias (N=96)

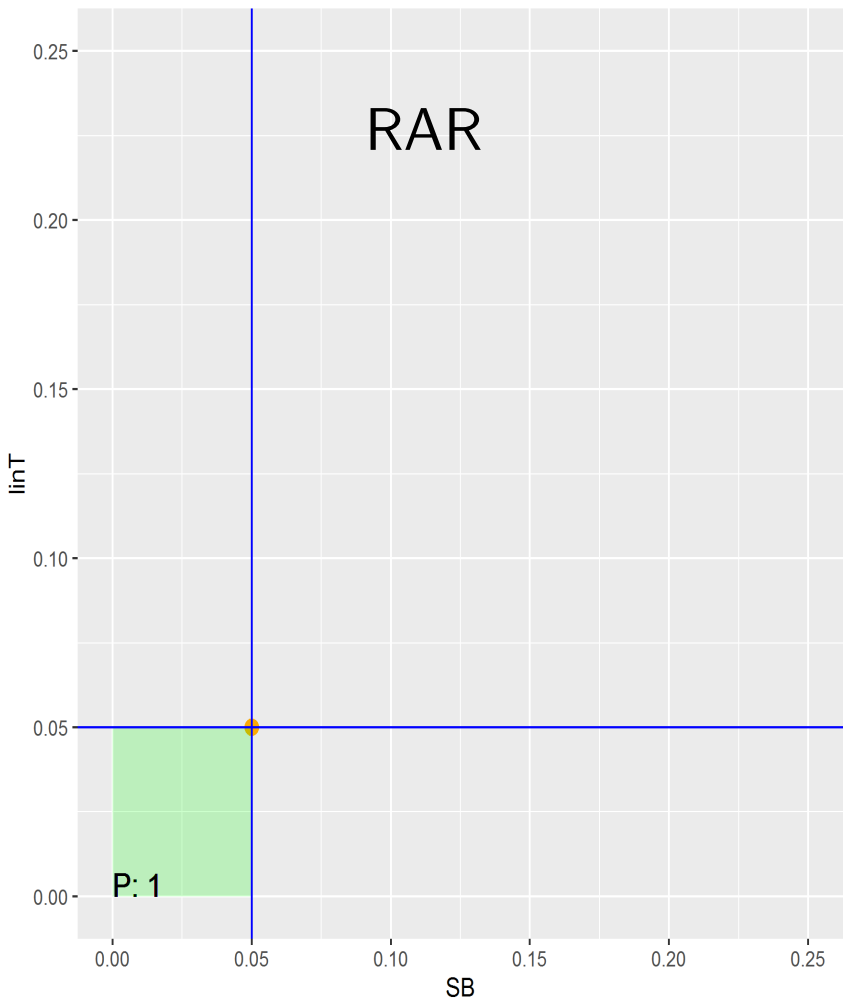
setting: $N_E = N_C = 48, \eta = 0; \theta = 1.0 \times \sigma$

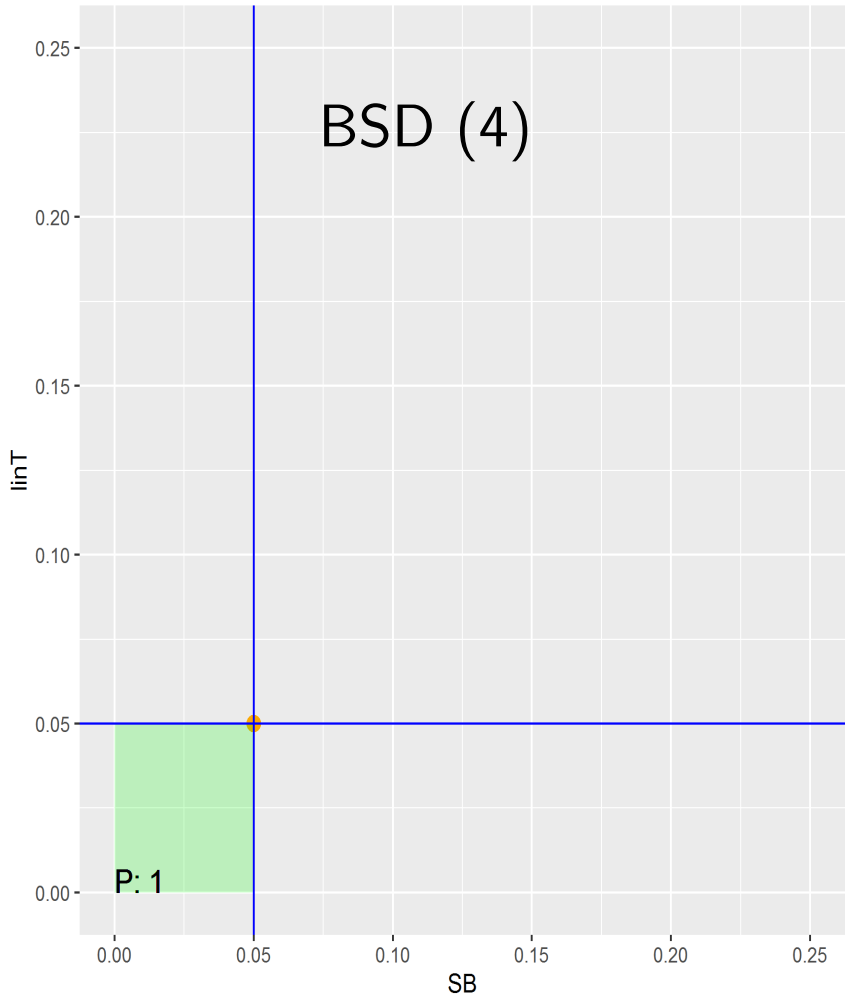




6. CSE - Result: Both Biases for (N=96)

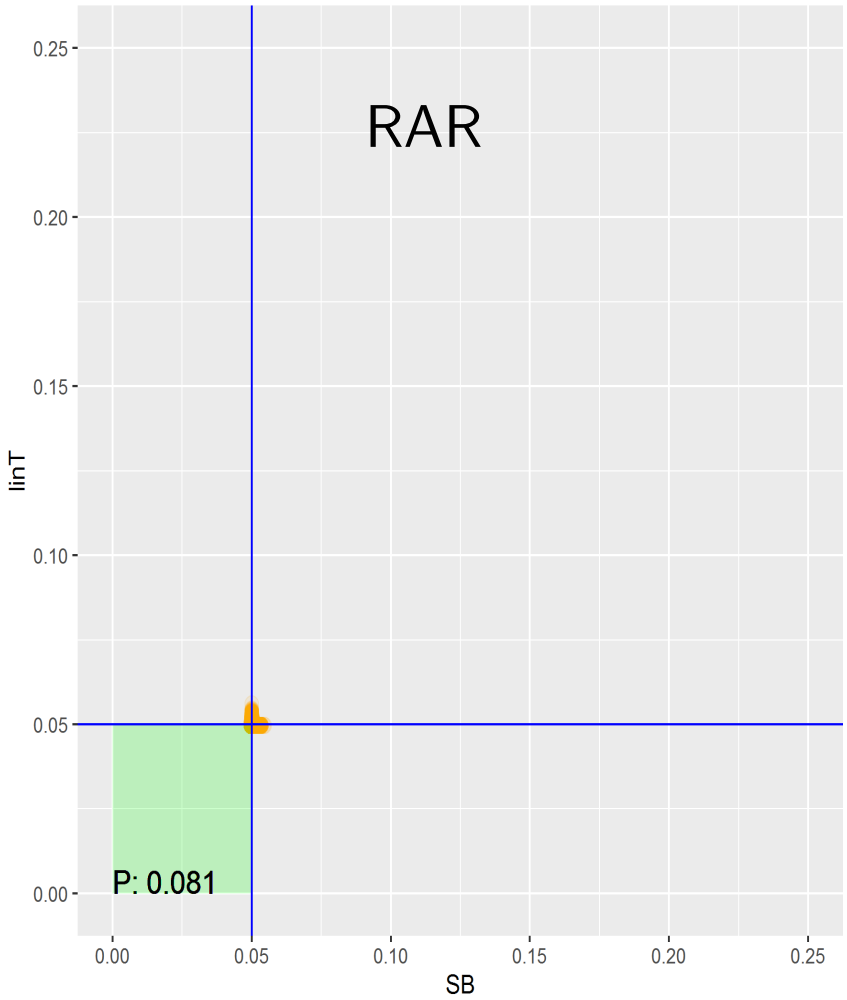
setting: $N_E = N_C = 48, \eta = 0.0 \times \delta,\ \theta = 0.0 \times \sigma$

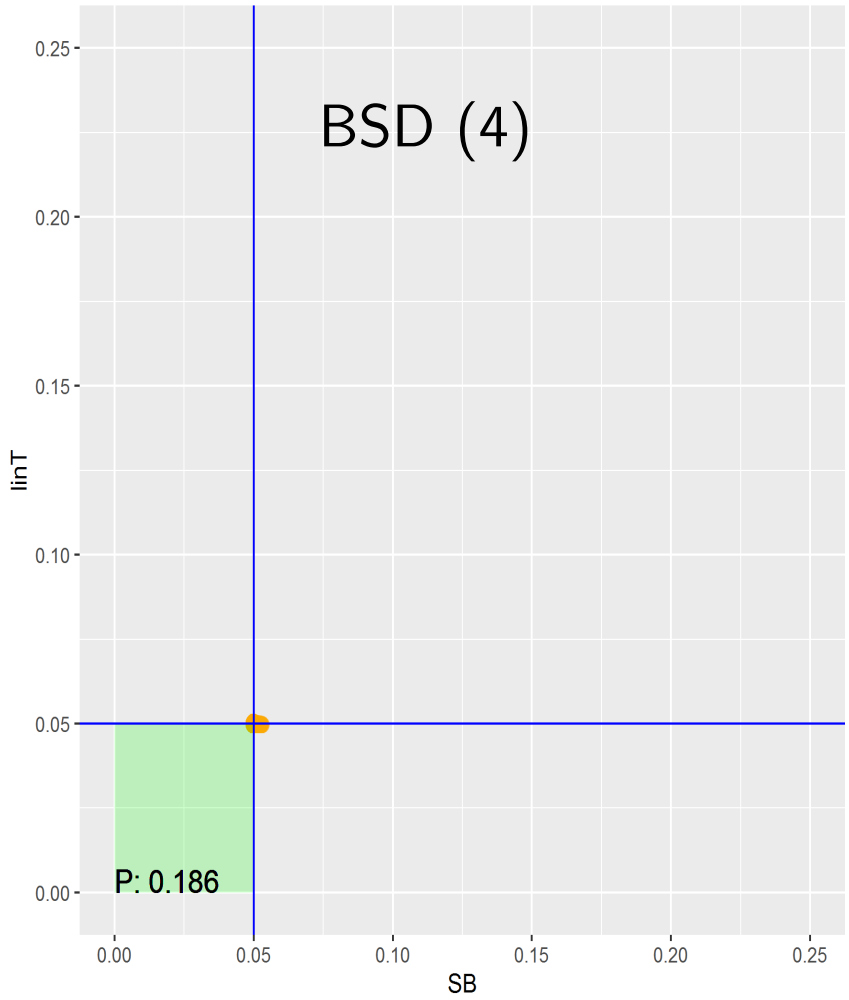




6. CSE - Result: Both Biases for (N=96)

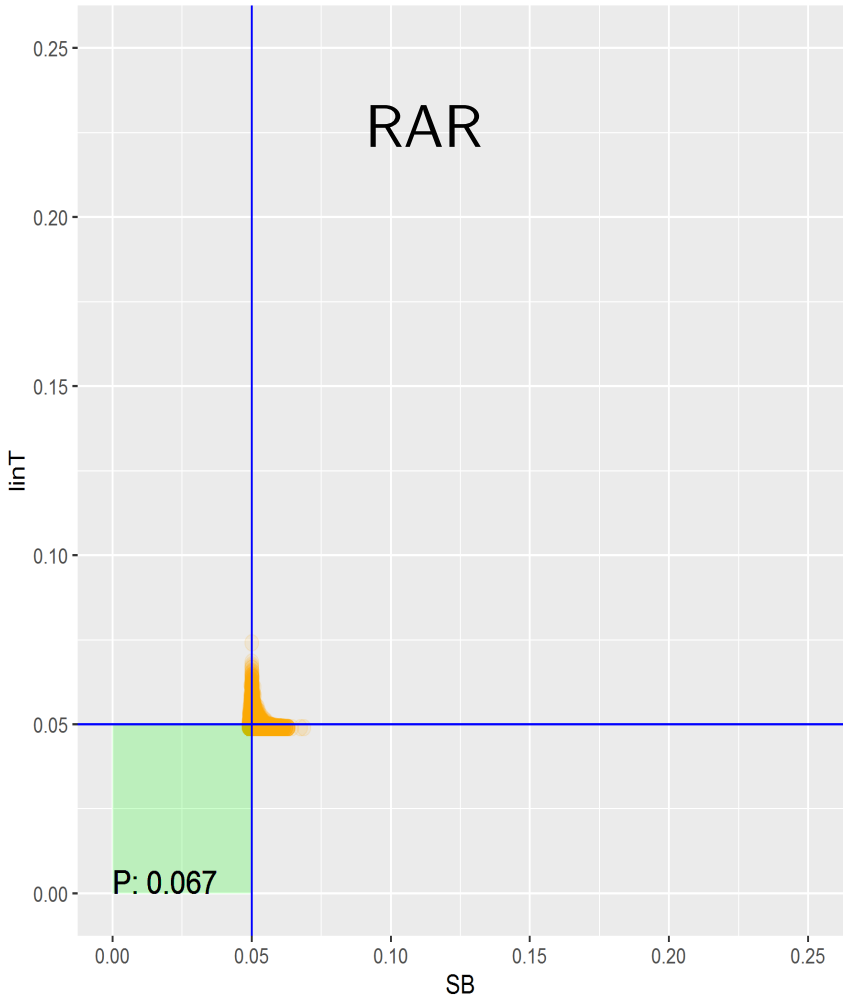
setting: $N_E = N_C = 48, \eta = 0.1 \times \delta, \theta = 0.2 \times \sigma$

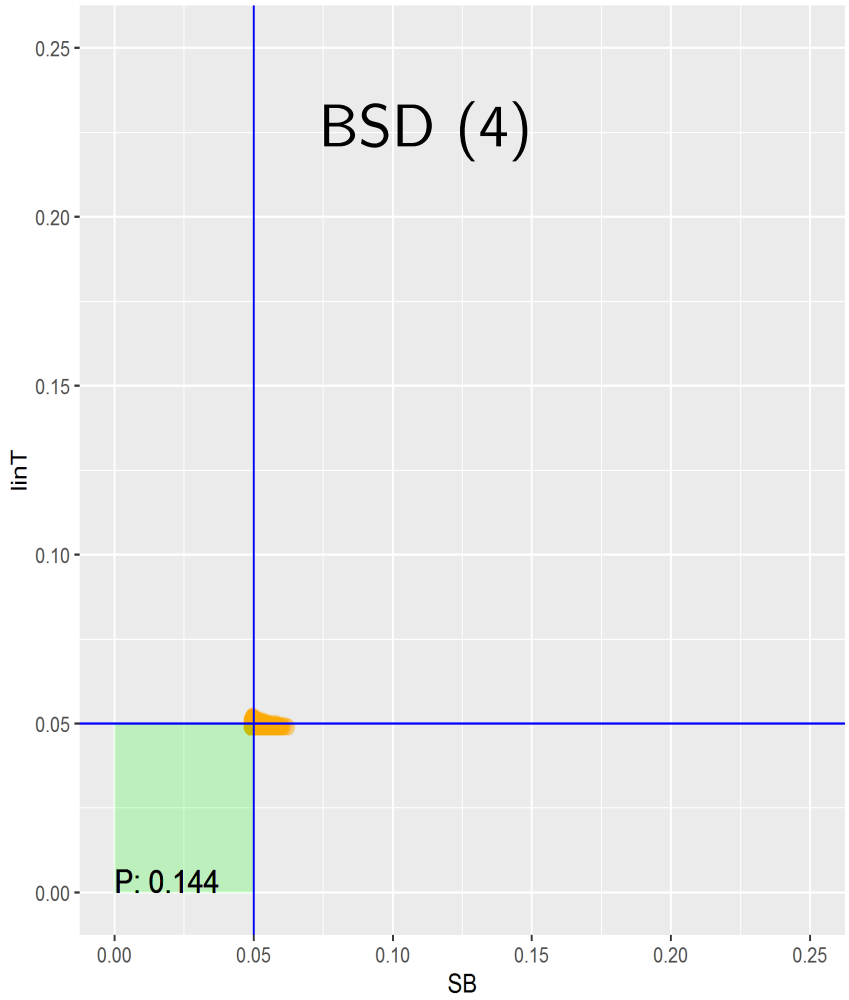




6. CSE - Result: Both Biases for (N=96)

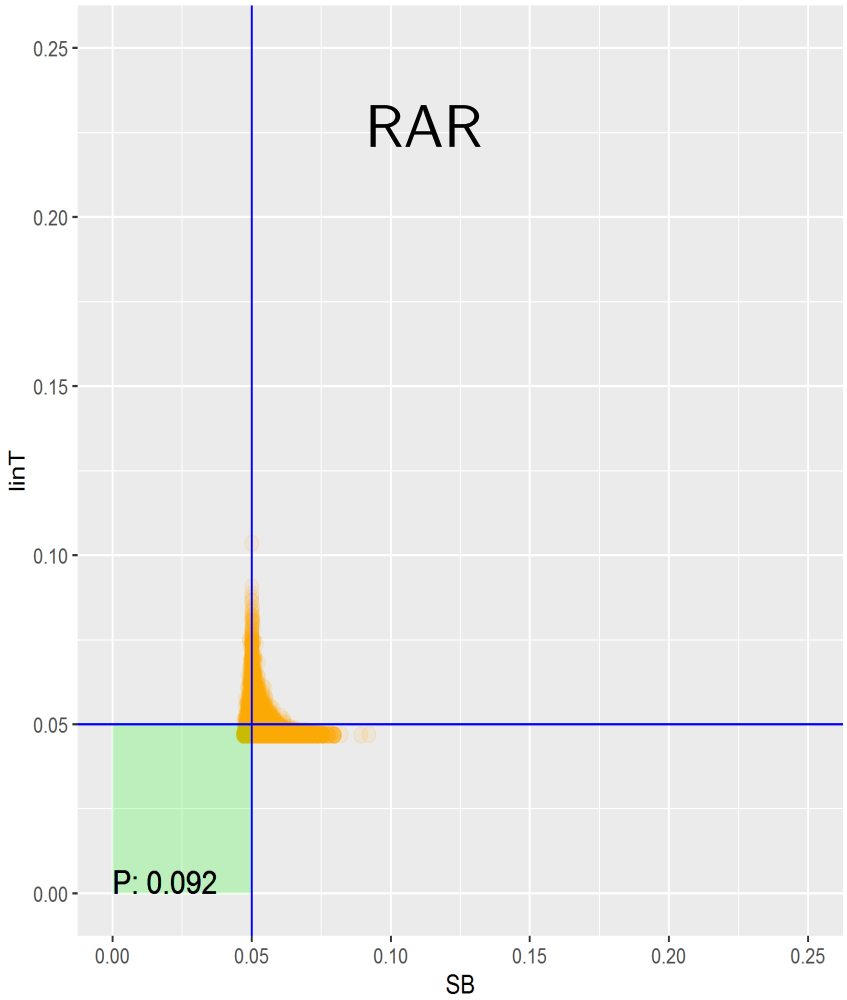
setting: $N_E = N_C = 48, \eta = 0.2 \times \delta, \theta = 0.4 \times \sigma$

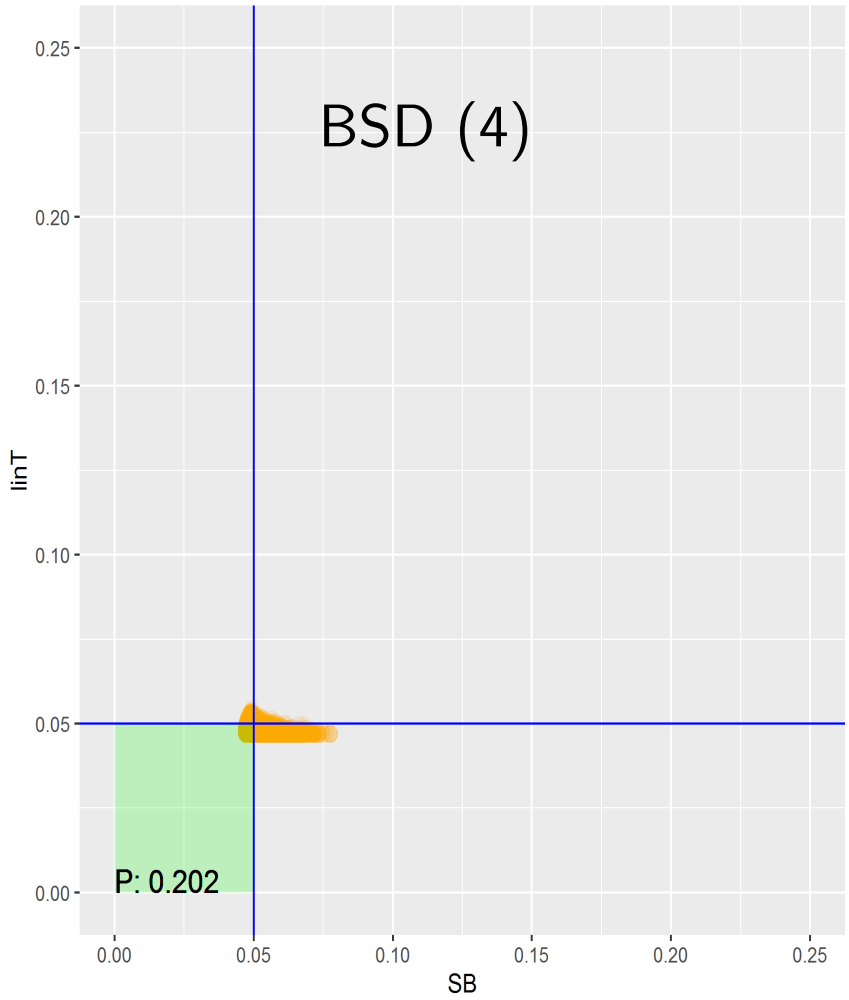




6. CSE - Result: Both Biases for (N=96)

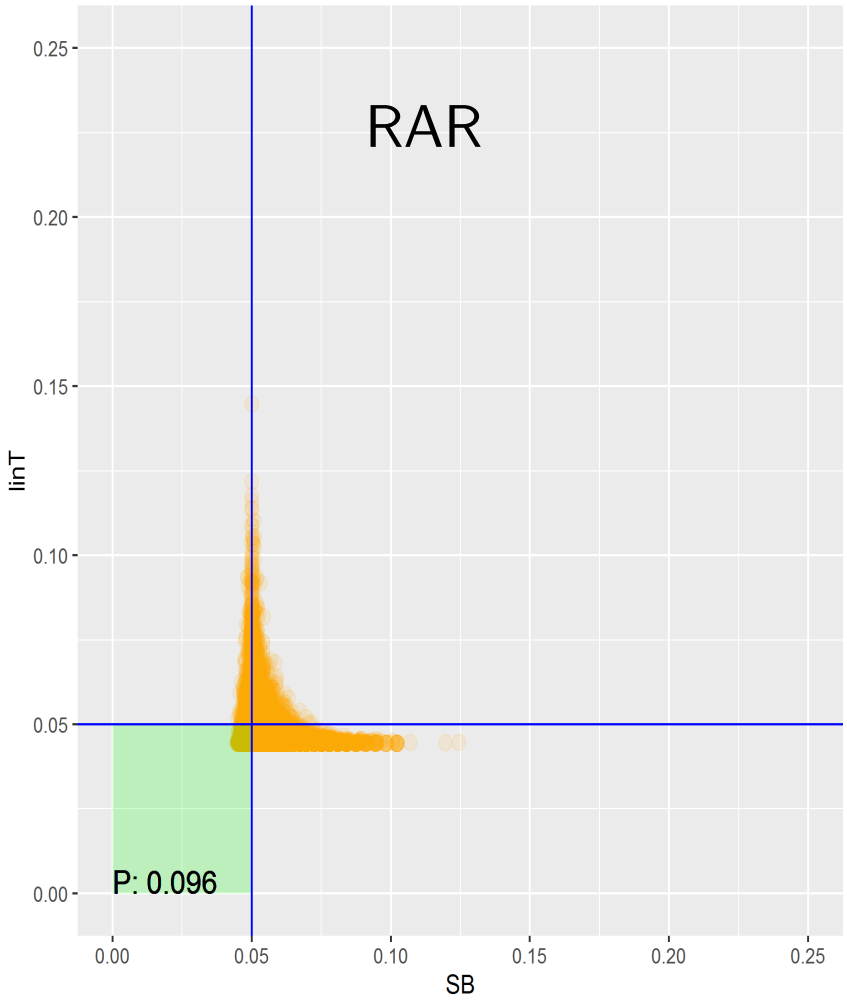
setting: $N_E = N_C = 48, \eta = 0.3 \times \delta, \theta = 0.6 \times \sigma$

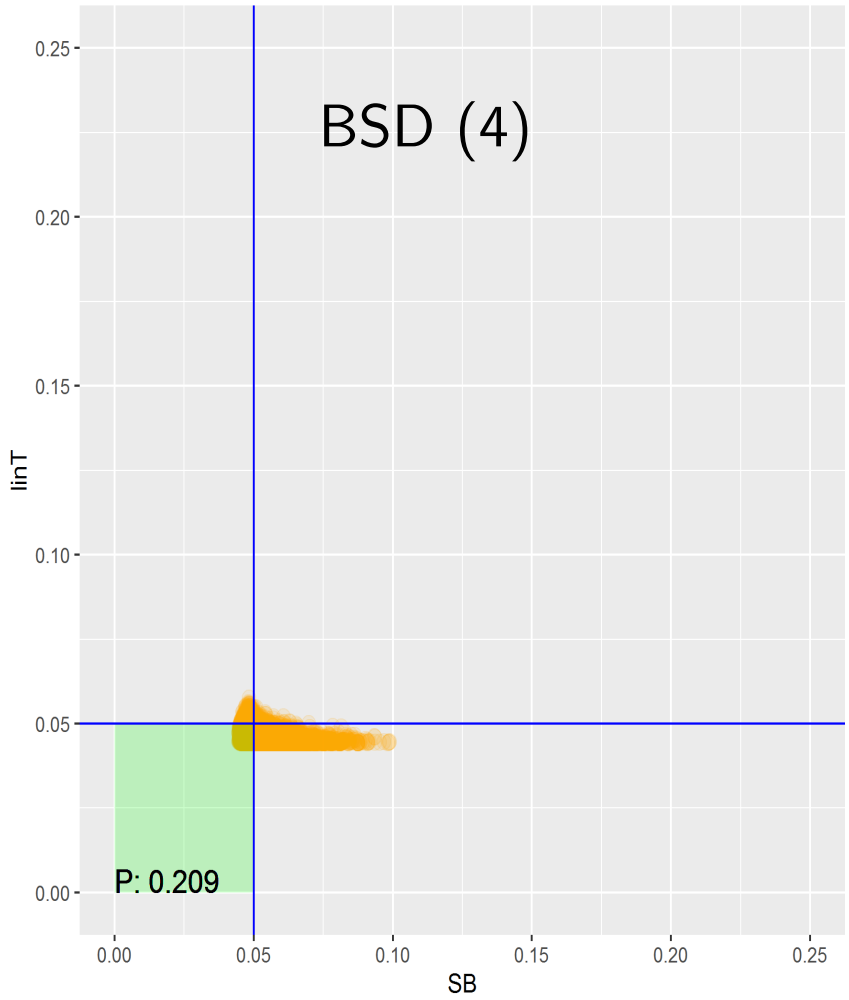




6. CSE - Result: Both Biases for (N=96)

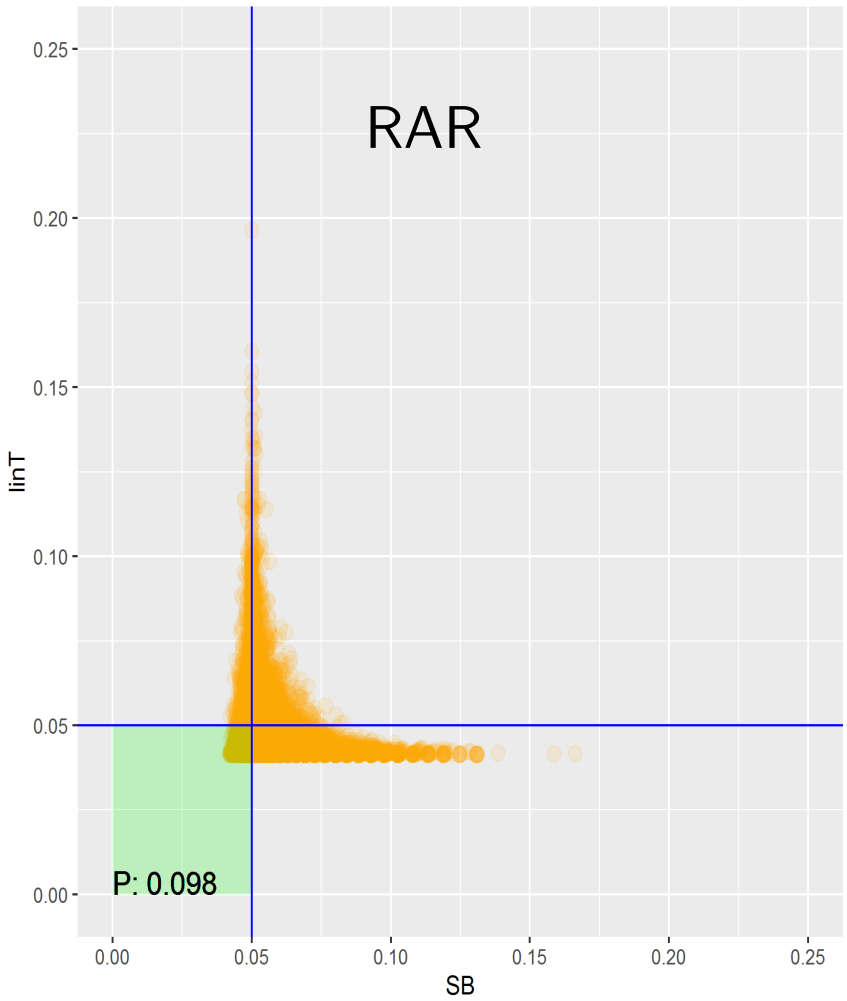
setting: $N_E = N_C = 48, \eta = 0.4 \times \delta, \theta = 0.8 \times \sigma$

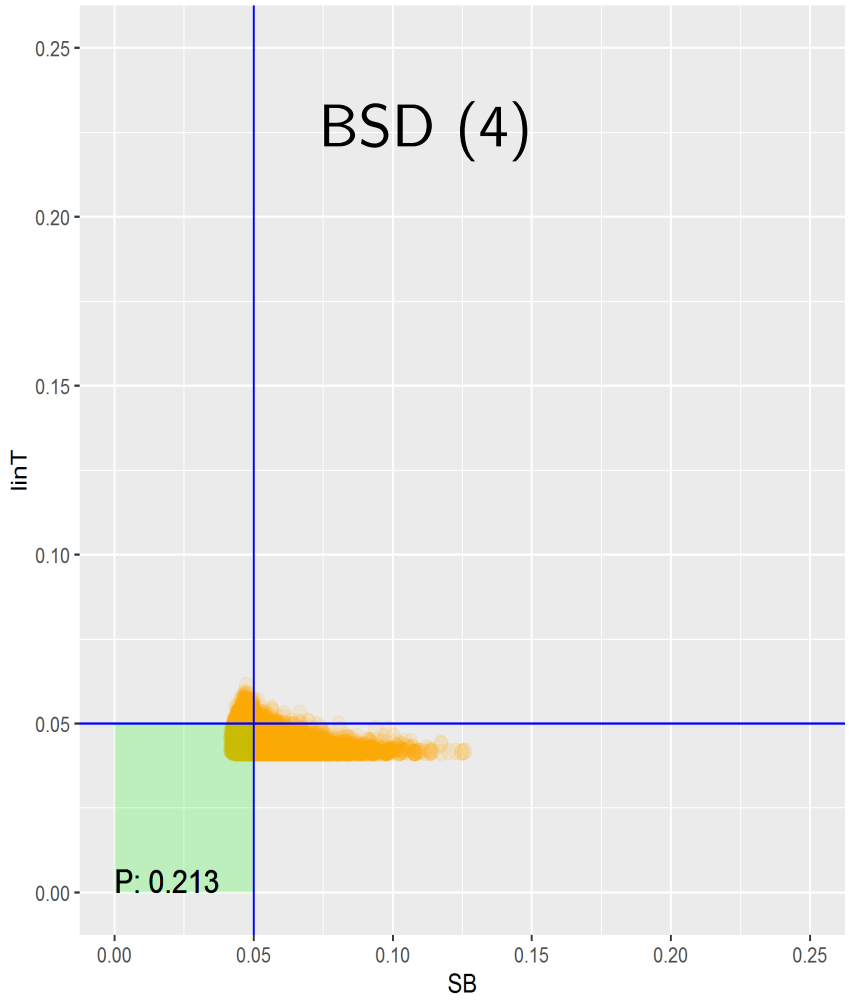




6. CSE - Result: Both Biases for (N=96)

setting: $N_E = N_C = 48, \eta = 0.5 \times \delta, \theta = 1.0 \times \sigma$





7. CSE - Discussion

Clinical implication

- ignoring the influence of selection bias may affect the test decision, by means of type-I-error rate probability
- the effect may be, that conservative or anticonservative test decisions occure
- in the context or rare diseases, this implies the risk to overlook an effective treatment

Conclusion

- presented a framework for scientific evaluation of randomisation procedures in the presence of bias, to be included in trial documents
- understand that the treatment effect could be hidden by bias, which may result from a randomisation sequence
- software to do assessment is available, R package *(randomizeR)*

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Conclusion

What is about other metrics / criteria?

- developed a uniform assessment criteria *(Schindler, 2016)*

Conclusion

What is about multiarm clincal trials?

- start understanding effects with multifactorial designs *(Tasche, 2015, Uschner, 2016)*

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Conclusion

What is about time to event endpoints?

- start understanding effects with time to event data *(Rückbeil, 2015)*

Conclusion

Open problems??

- start understanding the effect of missing values on the test decision based on randomisation test *(Heussen, 2016)*
- no yet completely developed a bias corrected test *(Kennes, 2015)*

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