Effects of publication bias and hidden multiplicity on reproducibility in biomedical discovery research

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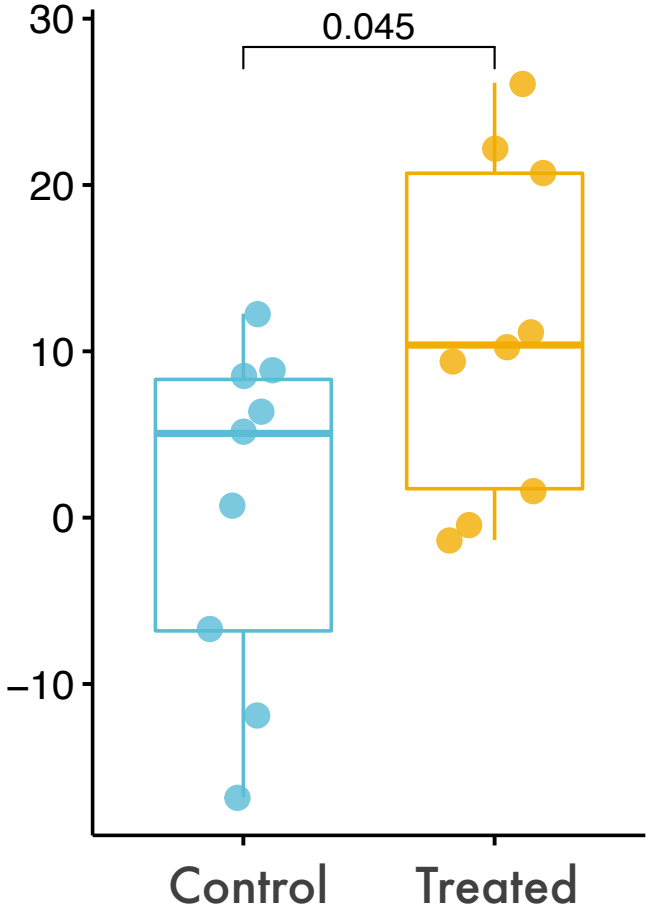
What is a good sample size for replicating a study?



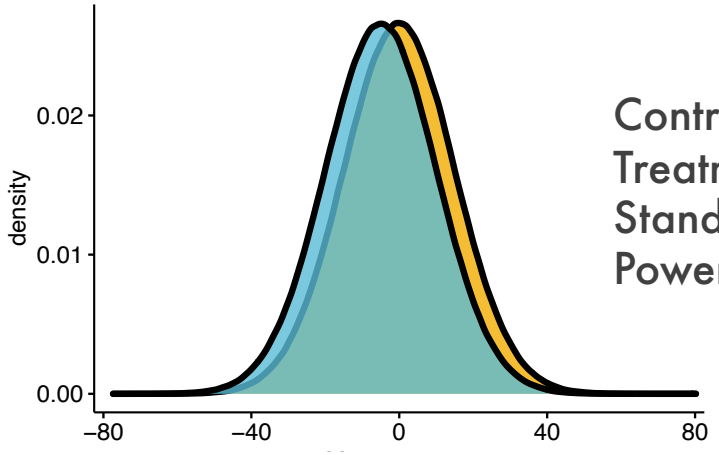
Published study:

- Compare 9 treated and 9 control mice
- Observed difference between means: 10 units
- Observed mean standard deviation: 10 units
- P-value: 0.049

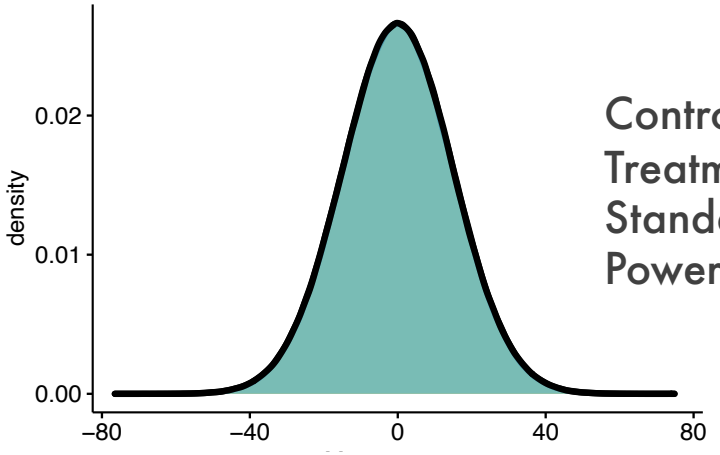
Problem:

How many animals should we use to achieve 80% power to detect a potential positive difference as statistically significant?

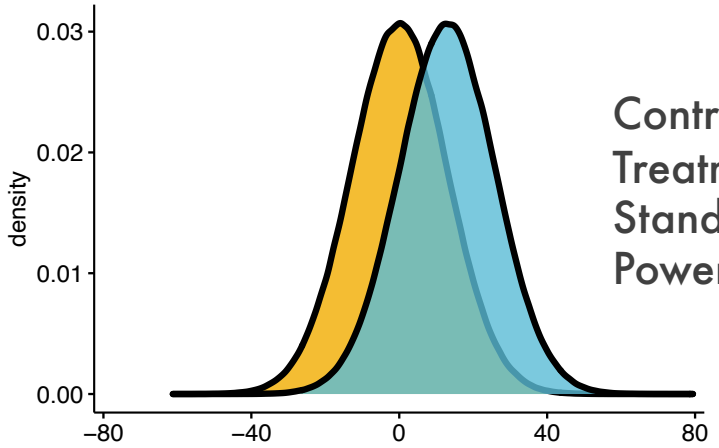
The observed results can arise from a variety of models



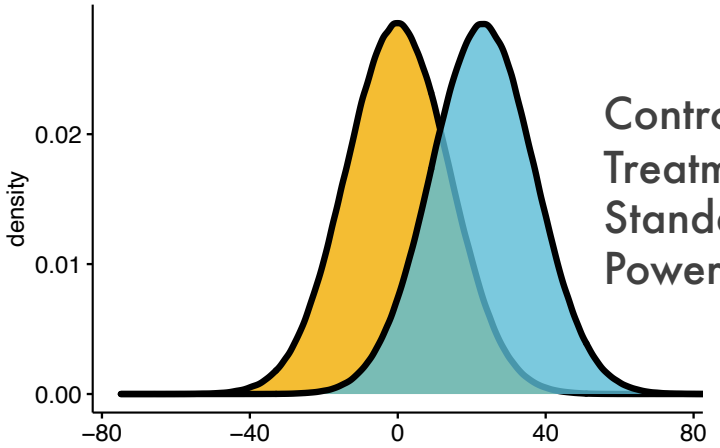
Control: N(0, 15)
Treatment: N(-5, 15)
Standard effect: -0.33
Power (N=12). 0.7%



Control: N(0, 15)
Treatment: N(0, 15)
Standard effect: 0
Power (N=12): 5%



Control: N(0, 13)
Treatment: N(13, 13)
Standard effect: 1.0
Power (N=12): 77%



Control: N(0, 14)
Treatment: N(23,14)
Standard effect: 1.64
Power (N=12): 99%

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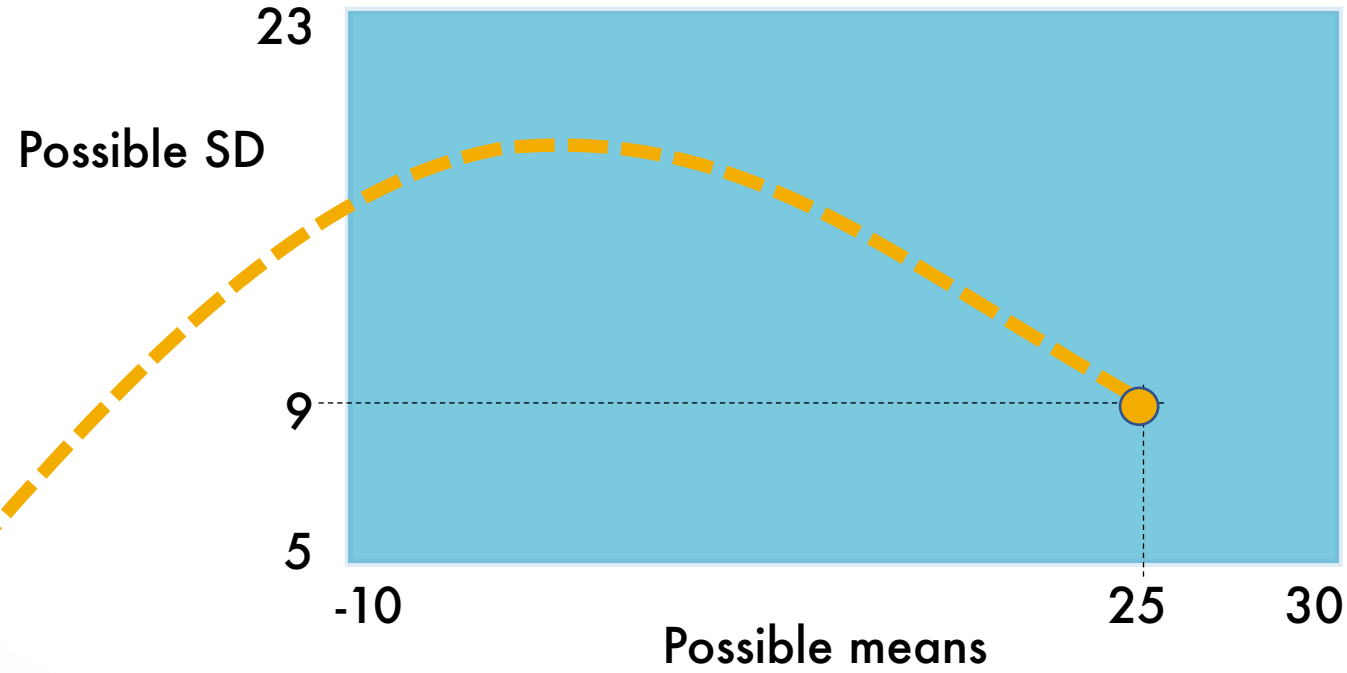
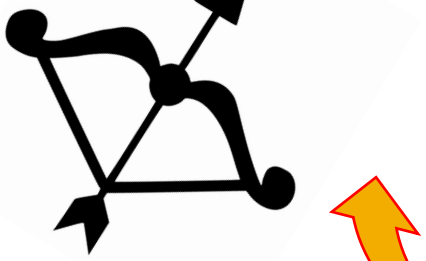
We used simulations to explore all possible model parameters



1



2

Draw a sample from:
1. N(25, 9) Treated
2. N(0, 9) Controls
Compare with prior results

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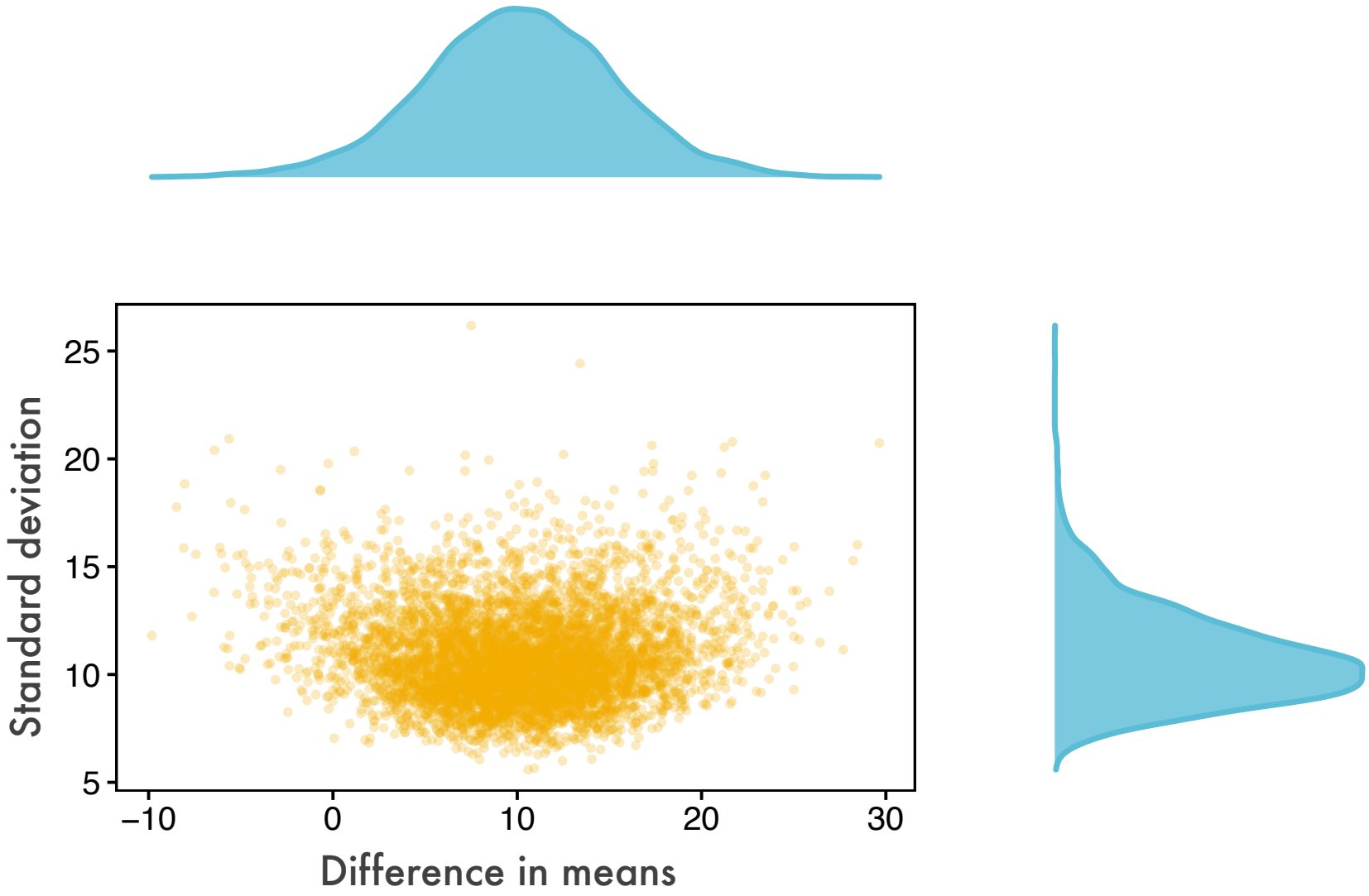
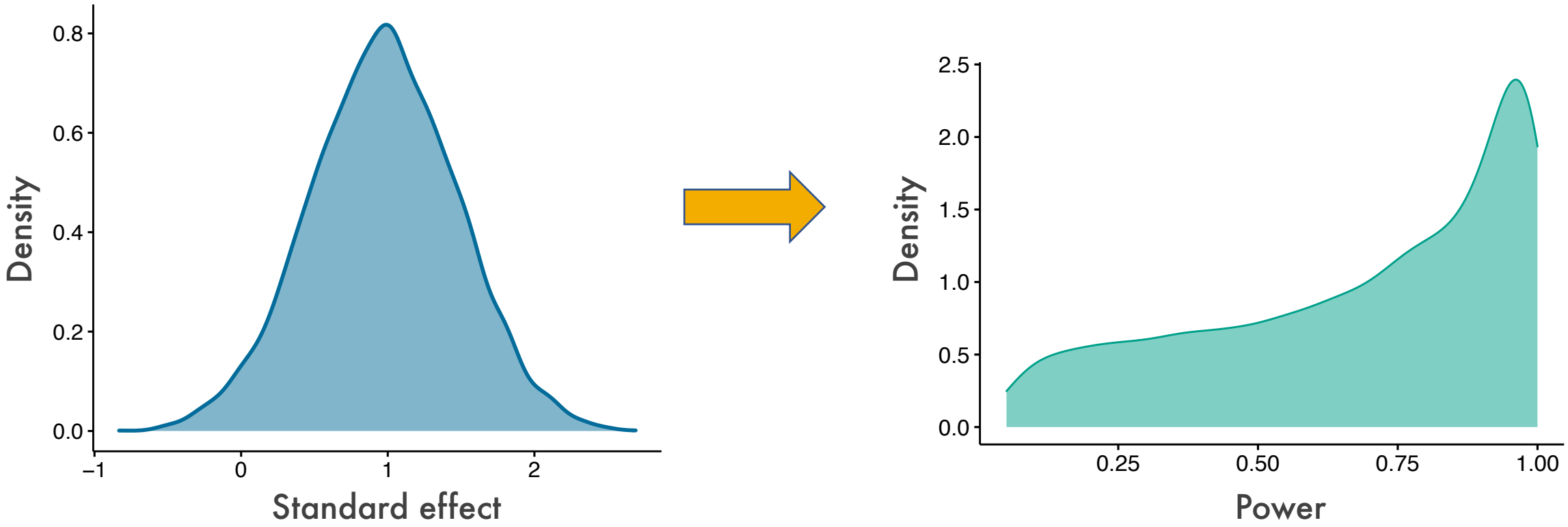
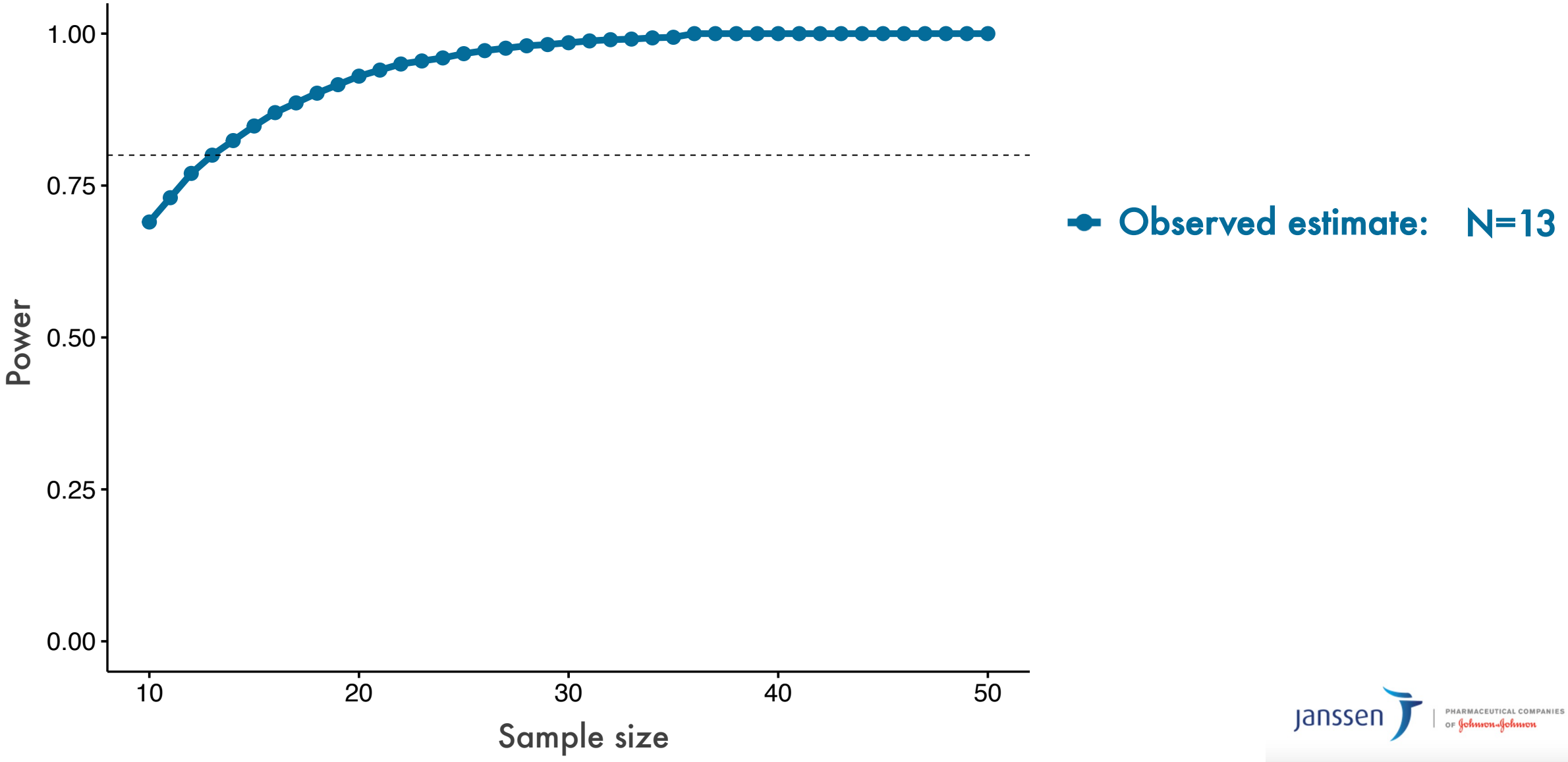
Different sets of model parameters can yield observed results



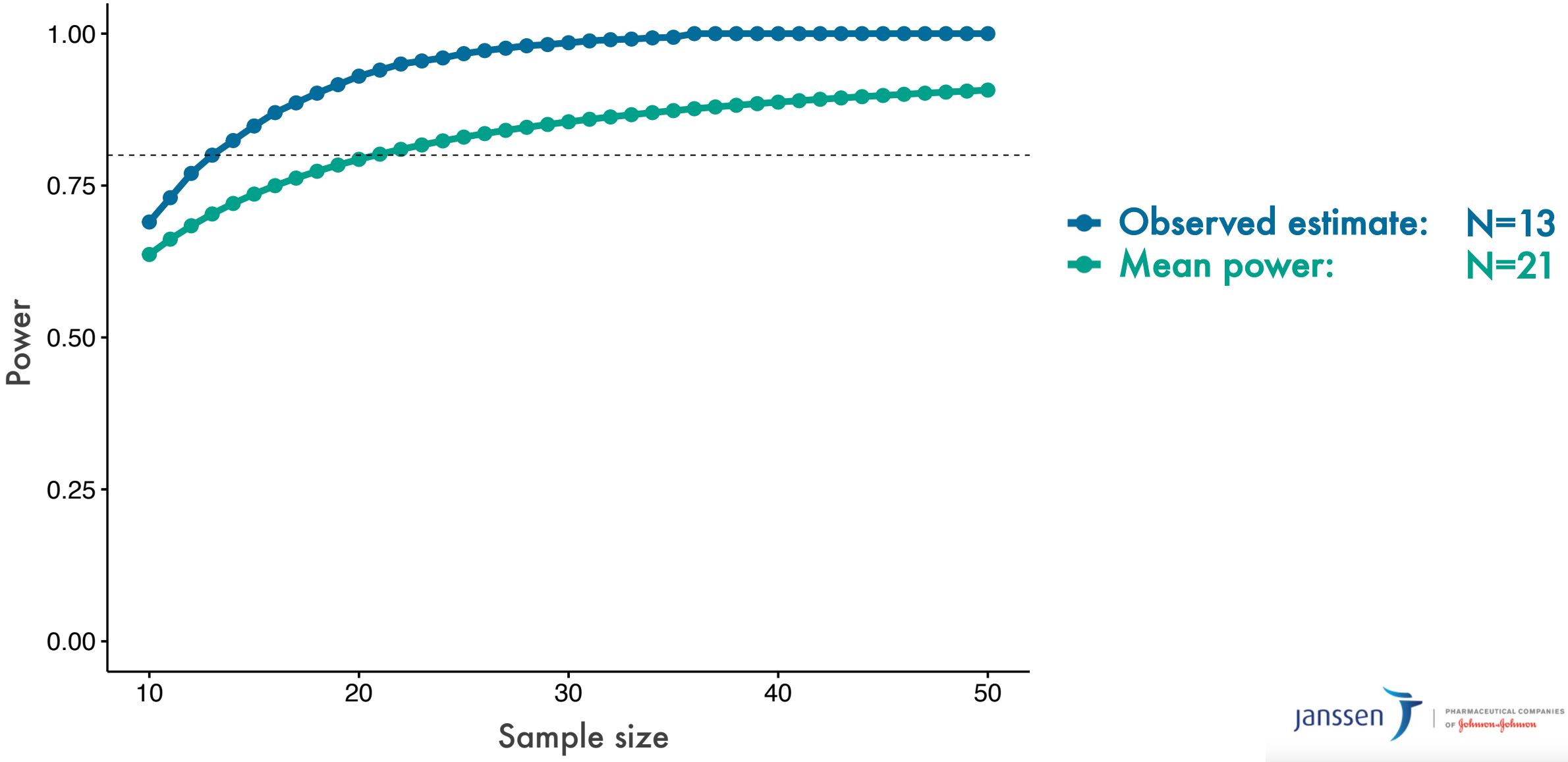
Treatment effects and power vary for each model



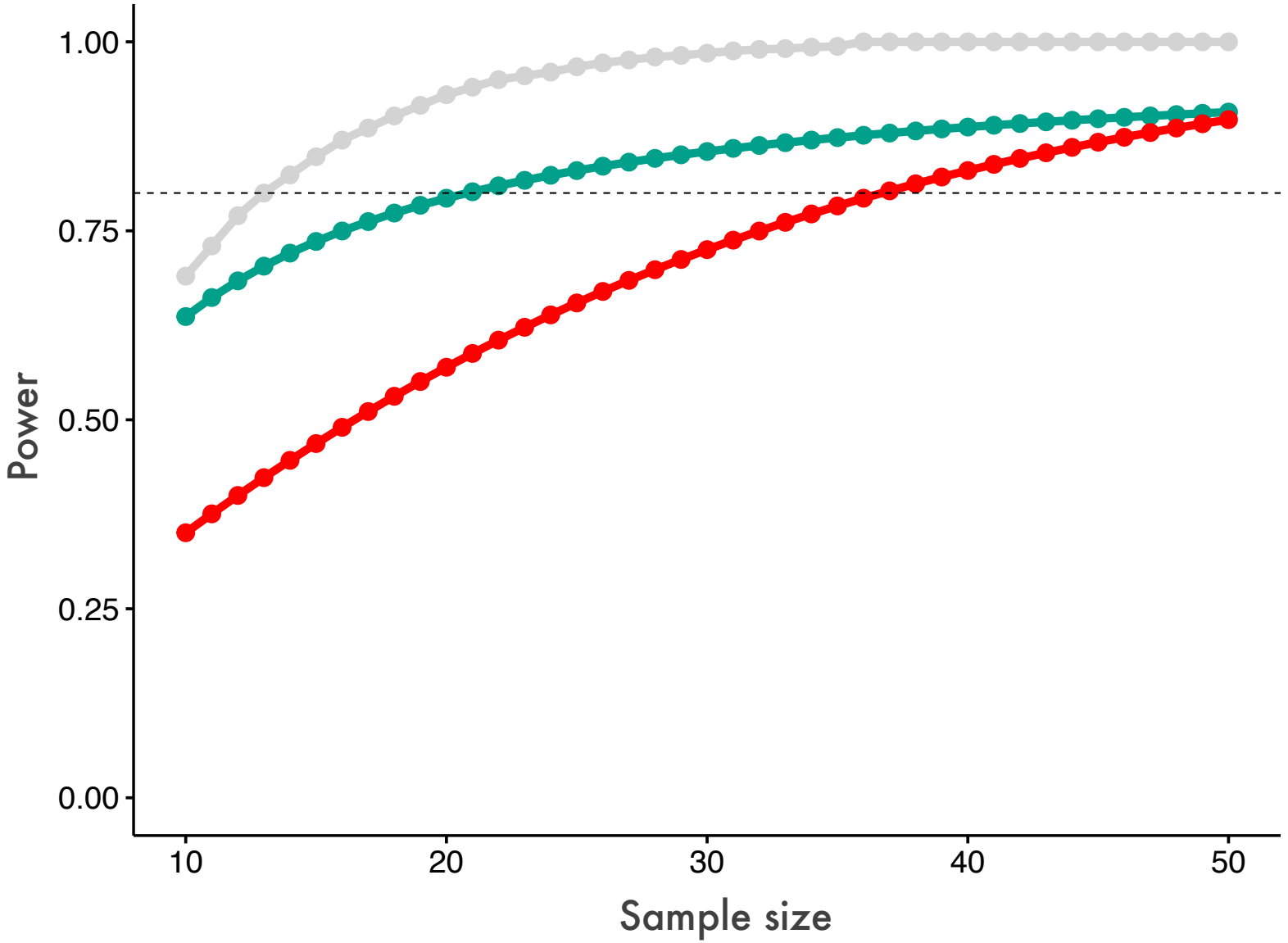
Most calculations assume observed effect is 'true' effect



Considering all possible models makes a difference



We can quantify the uncertainty of power calculations



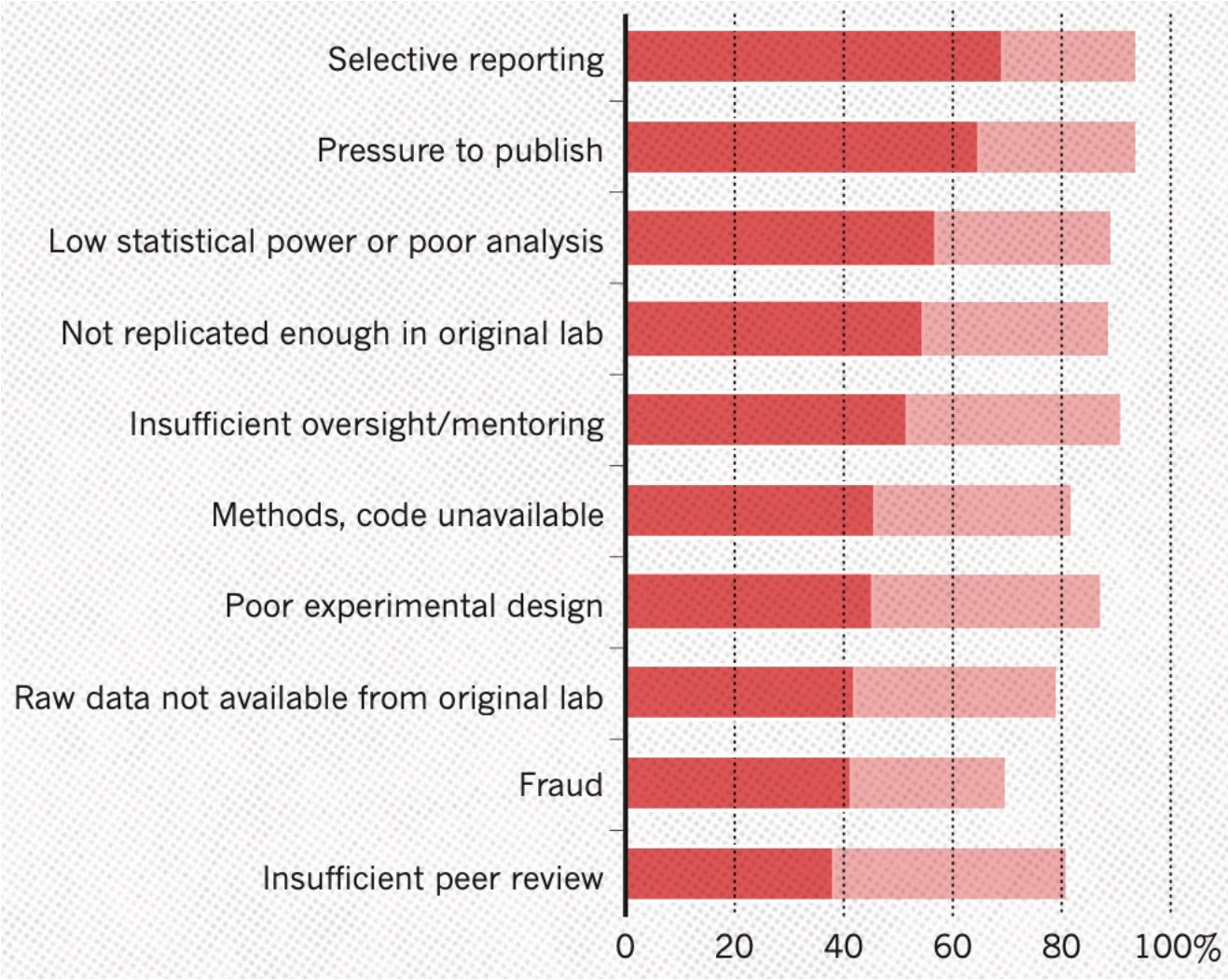
Observed estimate: N=13

Mean power: N=21

20th percentile: N=37

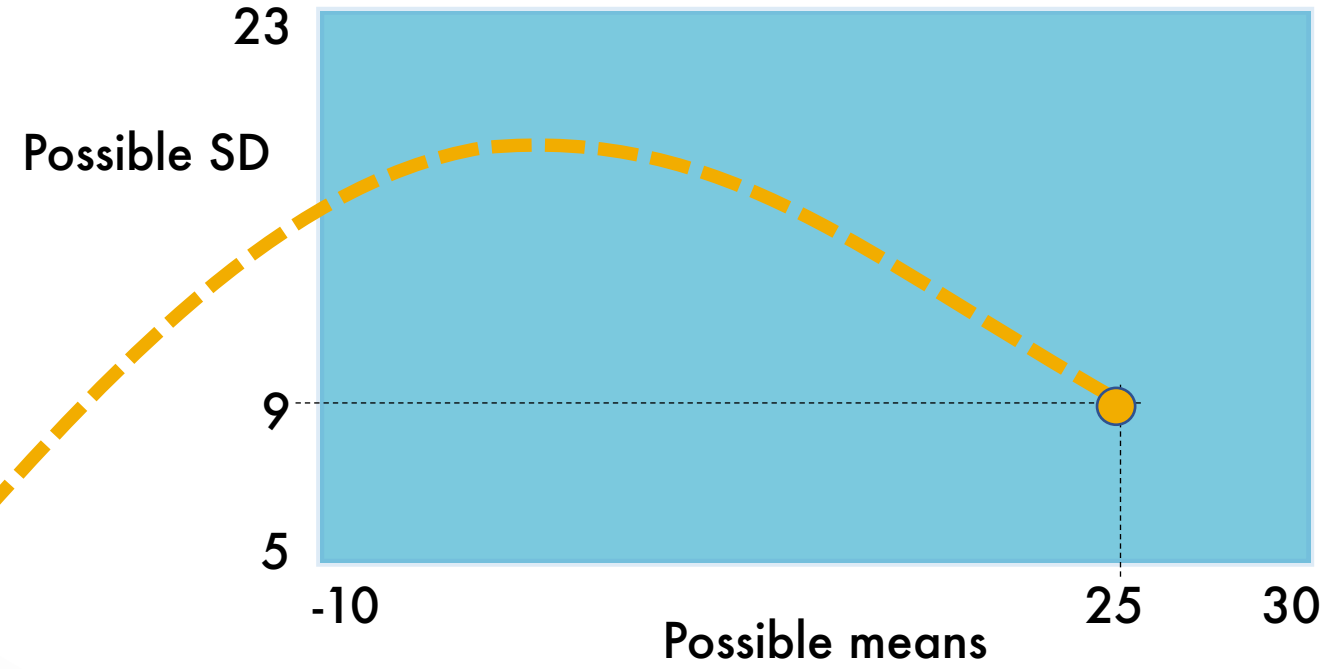
Publication bias and hidden multiplicity skew results

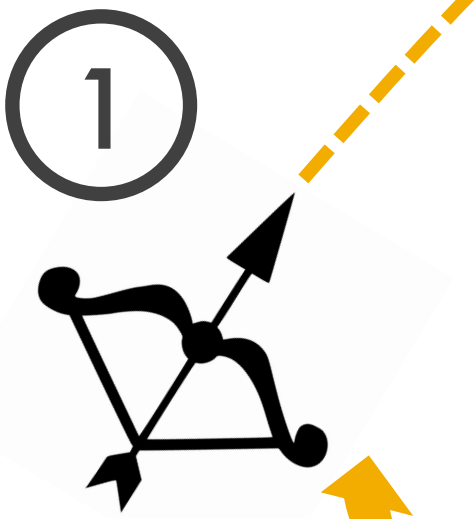
- 1M biomedical research papers published each year (2/minute)
- 7,600 medical research organizations in US alone
- Employ >100,000 people in US; >400,000 in Europe



Baker M., Is there a reproducibility crisis? Nature v. 533, 2016

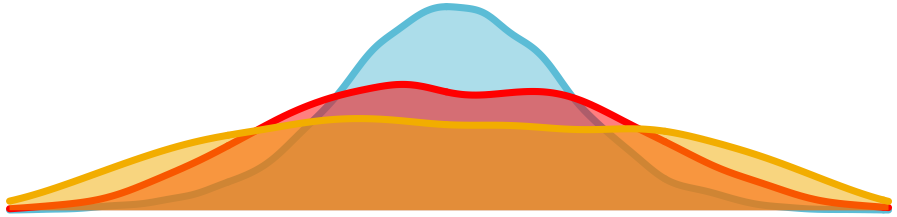
We modified our simulations to explore the effect of bias

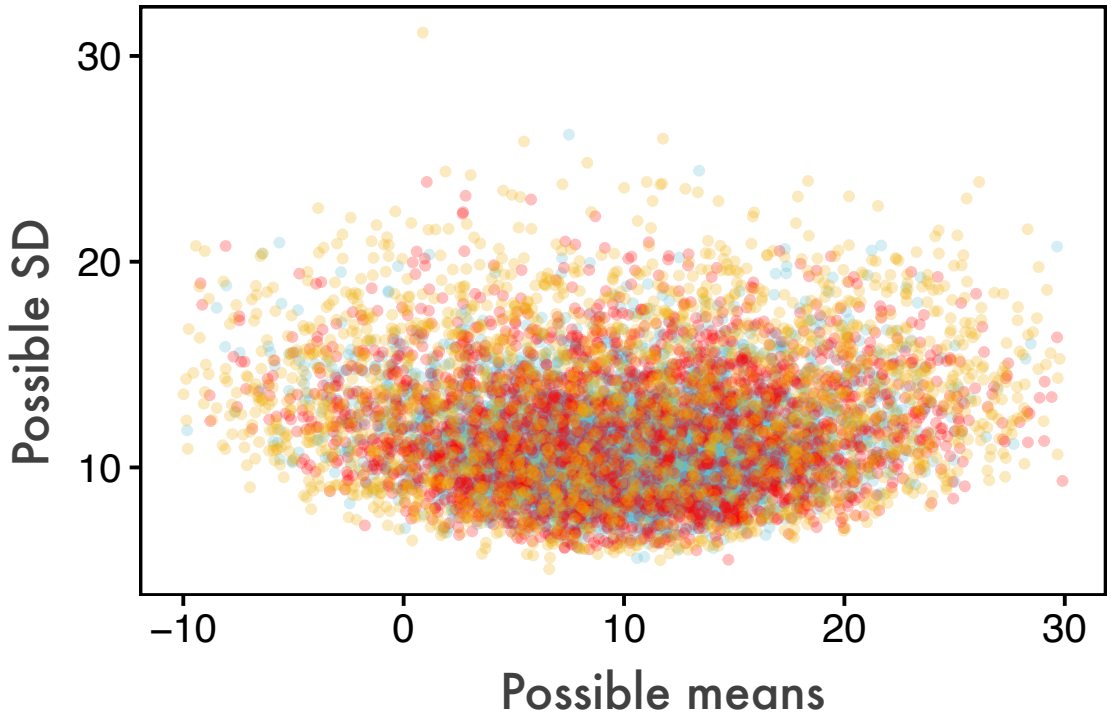


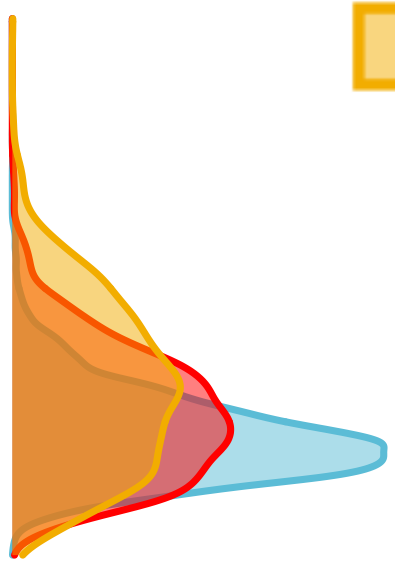


Draw many samples from:
1. N(25, 9) Treated
2. N(0, 9) Controls
Compare with prior results

Bias changes the distribution of possible parameters







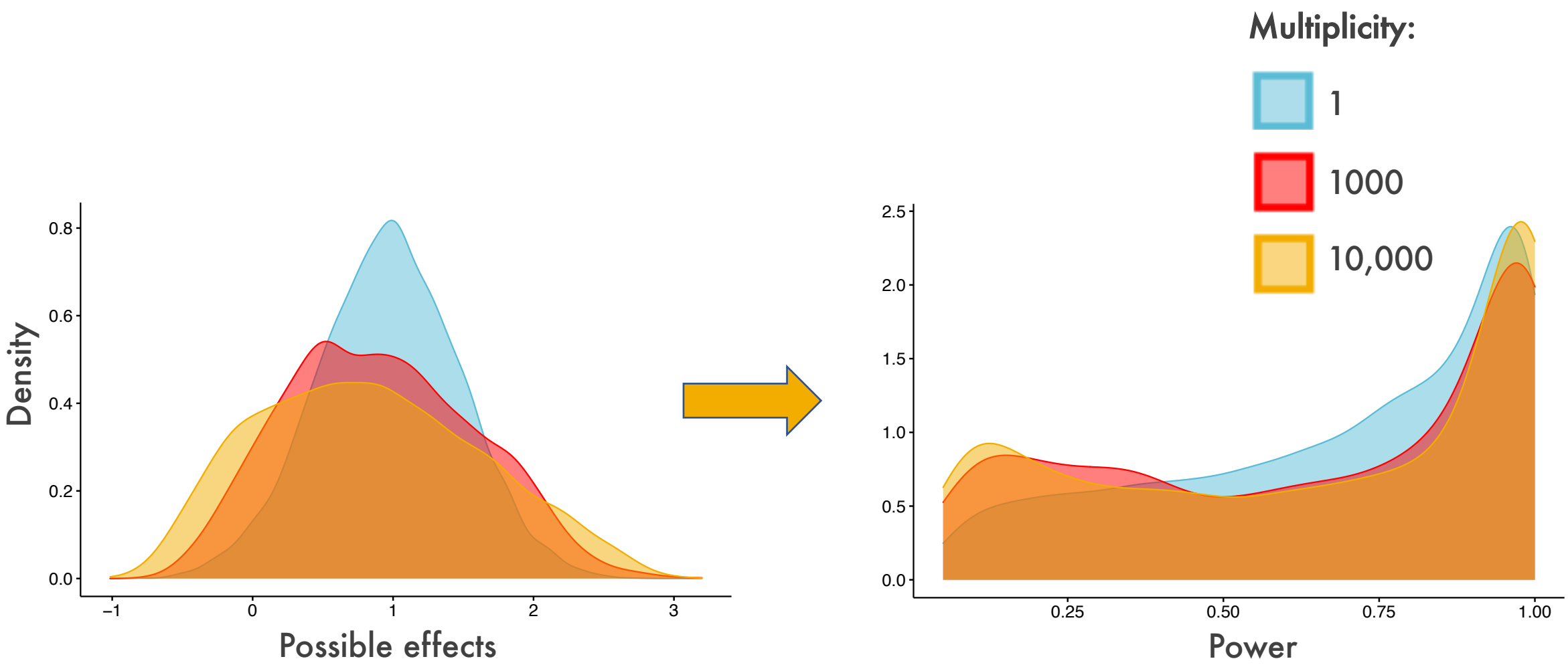
Multiplicity:

1

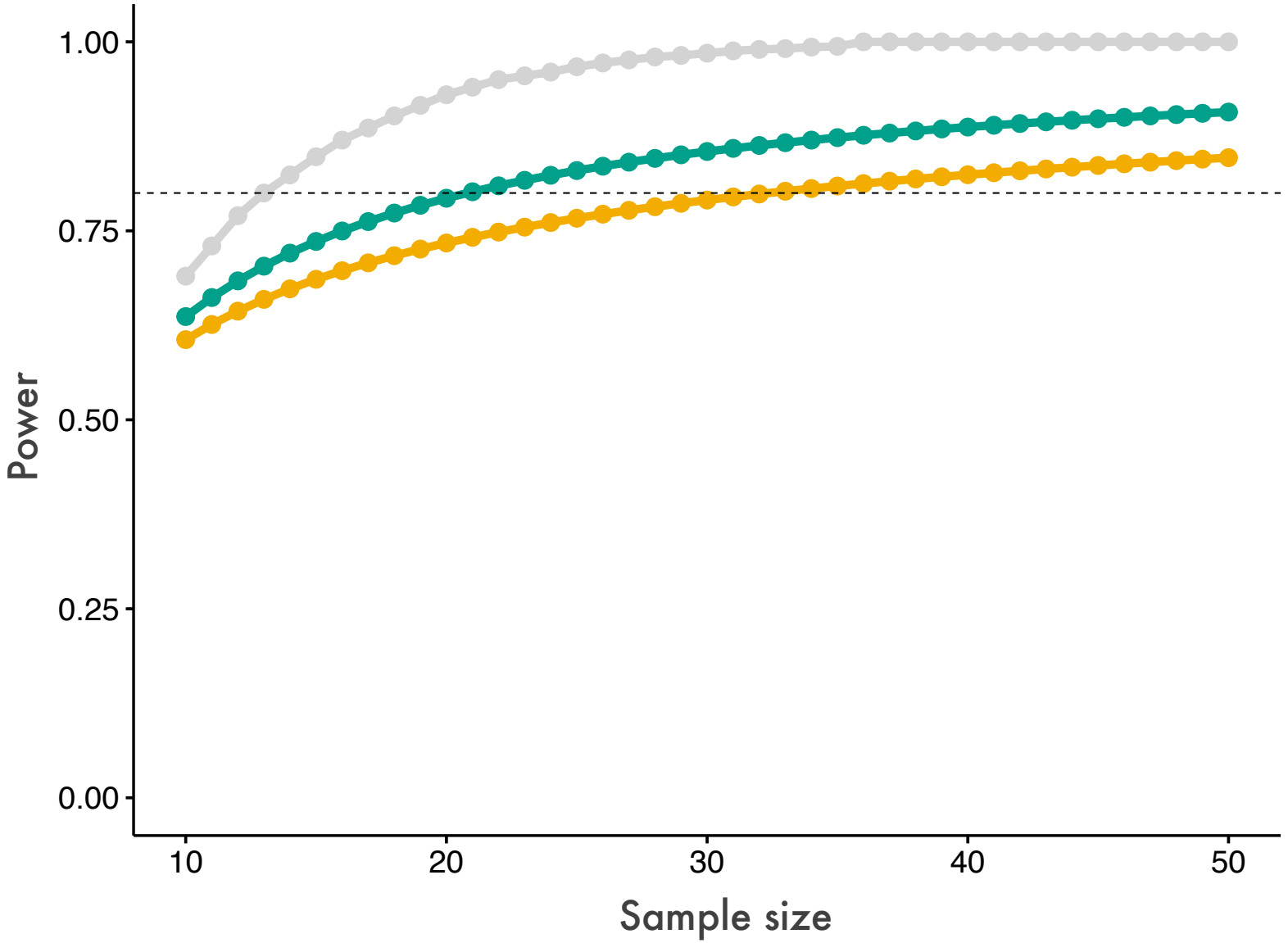
1000

10,000

Bias changes the distribution of possible effects and power



Publication bias necessitates larger samples



Observed estimate: N=13
Mean power: N=21
Low bias: N=32

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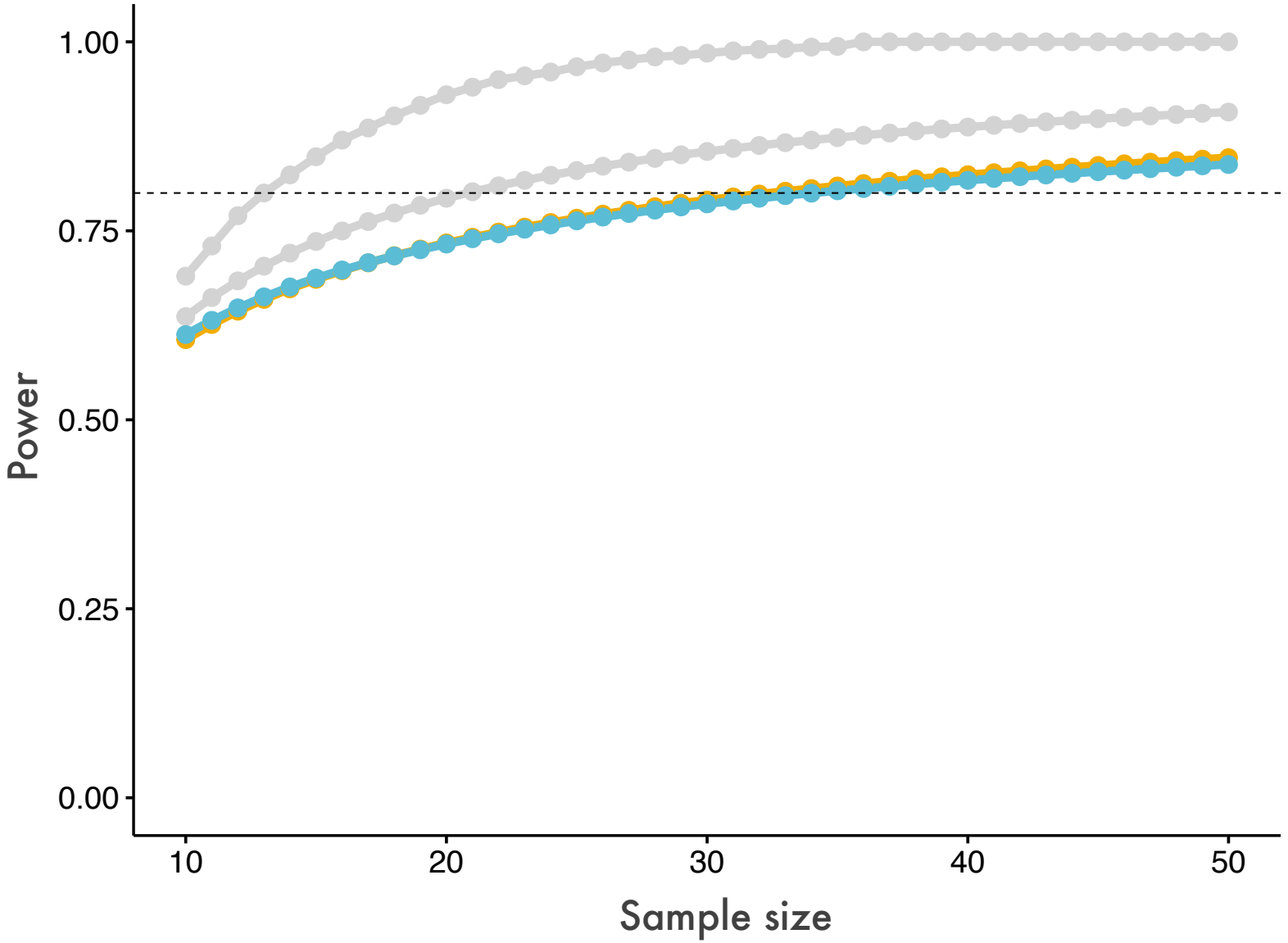

Observed estimate: N=13
Mean power: N=21
Low bias: N=32
High bias: N=34

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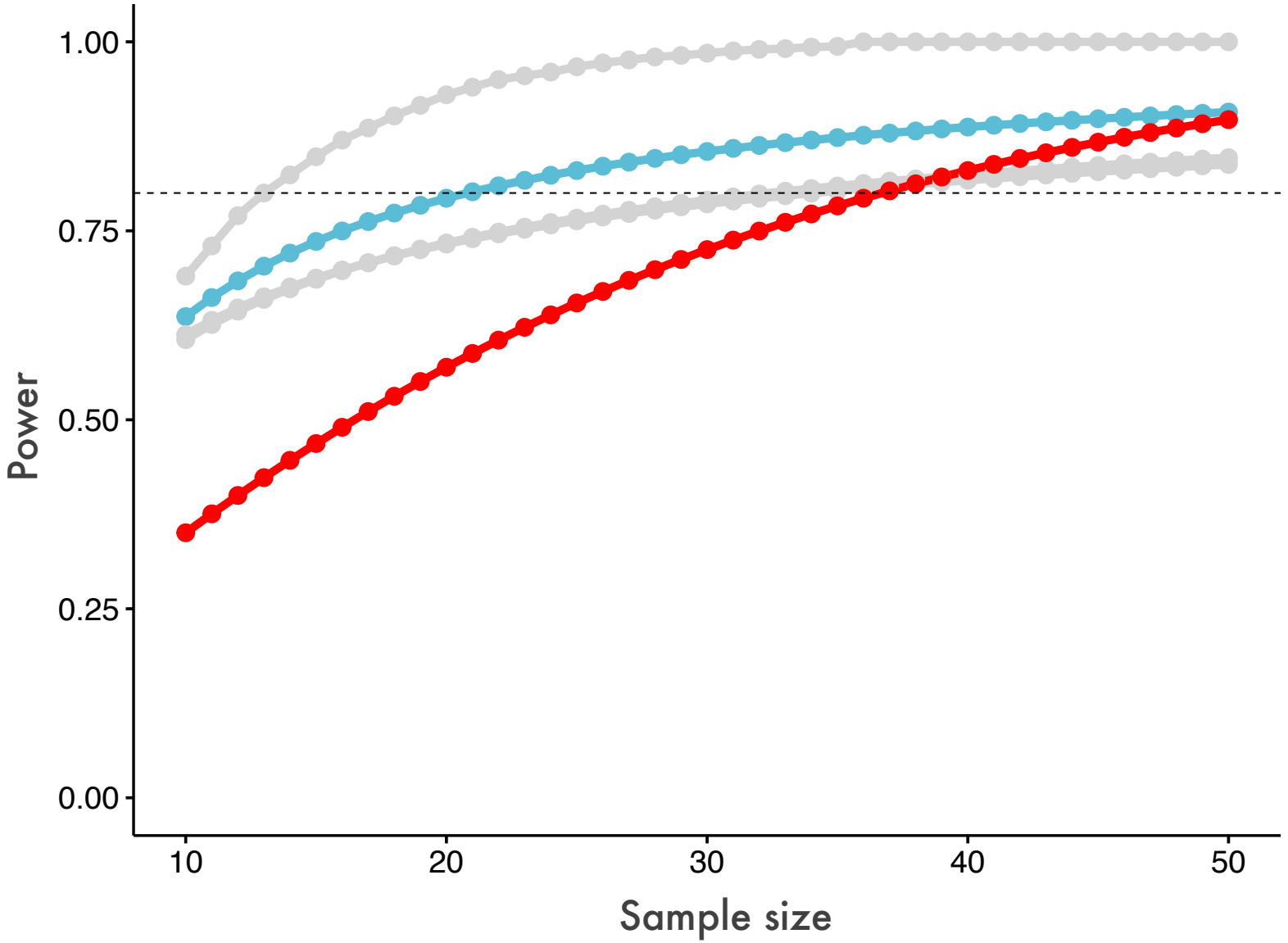

Observed estimate: N=13
Mean power: N=21
Low bias: N=32
High bias: N=50
20th percentile: N=37

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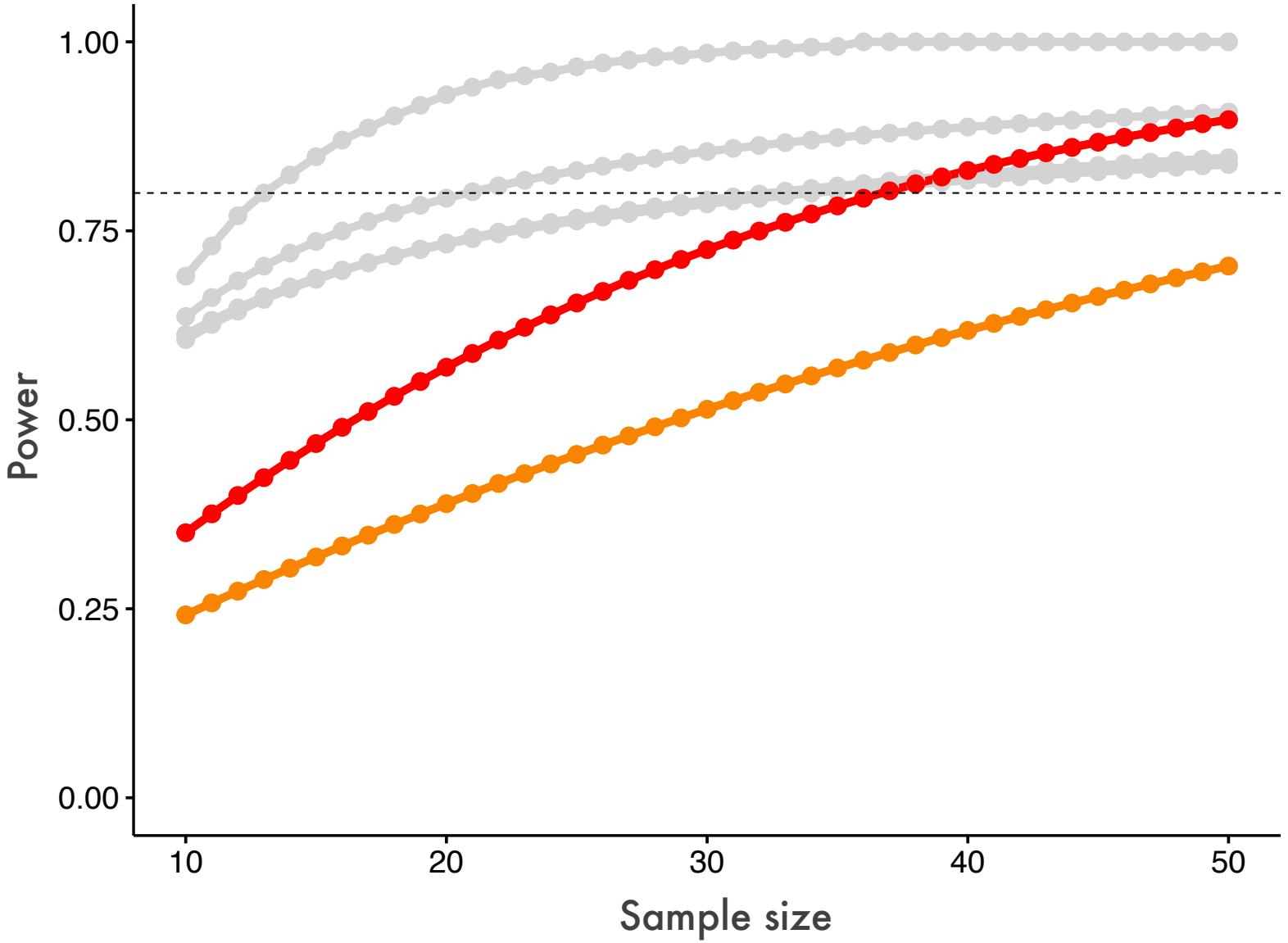

Observed estimate: N=13
Mean power: N=21
Low bias: N=32
High bias: N=34
20th percentile: N=37
Low bias: N=65

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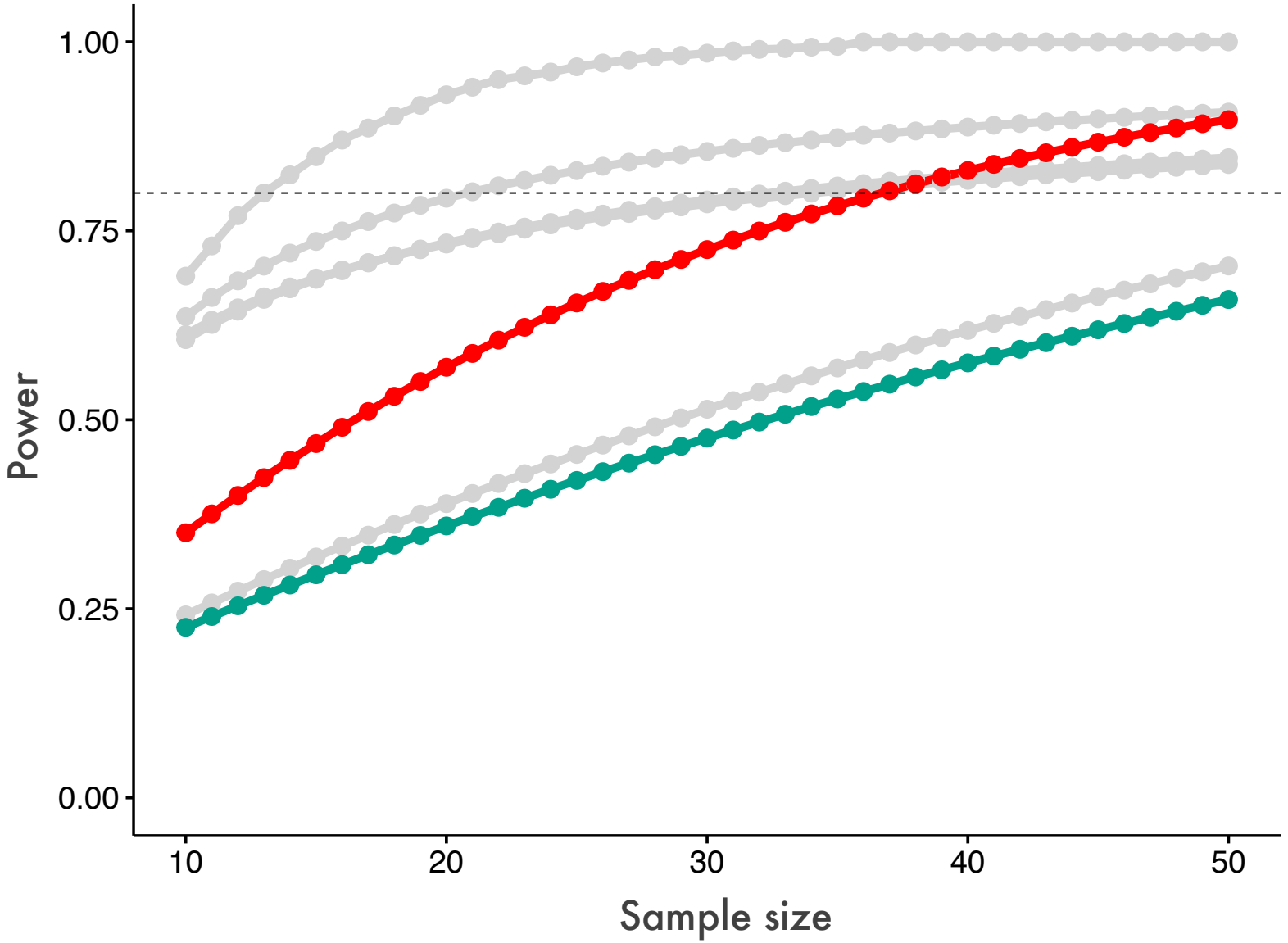

Observed estimate: N=13
Mean power: N=21
Low bias: N=32
High bias: N=34
20th percentile: N=37
Low bias: N=65
High bias: N=73

Replications require large sample sizes

- Assuming observed parameters reflect reality leads to underpowered studies
- P-values are not the only problem; estimates can vary in magnitude, direction
- The proposed method can be tailored to a given replication study
    - Uses all available information, can extend to unequal variance
    - Quantifies uncertainty in power calculation
    - Accommodates publication bias and hidden multiplicity
    - Can be computationally intensive