Power and sample size calculations

NORBIS Genestat course

Miriam Gjerdevik

Centre for Fertility and Health, NIPH

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Hypotheses

- Research questions to be addressed in a study are formulated as hypotheses
- During the planning stage of a study, one has to consider whether relevant quantities can be estimated with sufficient precision and if the study can give conclusive answers to the specified hypotheses
- Basically, larger sample size increases the precision of an estimate, i.e., the confidence interval narrows

Hypotheses

The null hypothesis, H_0

- The "no change" hypothesis, e.g., no association between the SNP and disease

The alternative hypothesis, H_1

- The "opposite" of H_0, e.g., there is an association between the SNP and disease

Possible conclusions of a study

There are two ways in which one can conclude from a statistical test:

- Reject H_0, e.g., there is an association between the SNP and disease
- Fail to reject/accept H_0, e.g., there is no association between the SNP and disease

Error types

Two types of errors in hypothesis testing

		Decision	
		Do not reject H_0	Reject H_0
Truth	H_0 is true	Correct decision	Type I error
	H_0 is false	Type II error	Correct decision

Significance level

Significance level (α):

- Probability of making a Type I error
- A low significance level protects against falsely rejecting H_0
- Usually, $\alpha = 0.05$ for test of a single hypothesis

Statistical power

Statistical power

- The probability of making a Type II error given an effect size Δ is denoted by $\beta(\Delta)$
- The statistical power given an effect size Δ is denoted by $\Pi(\Delta)$ and is related to $\beta(\Delta)$ by the formula

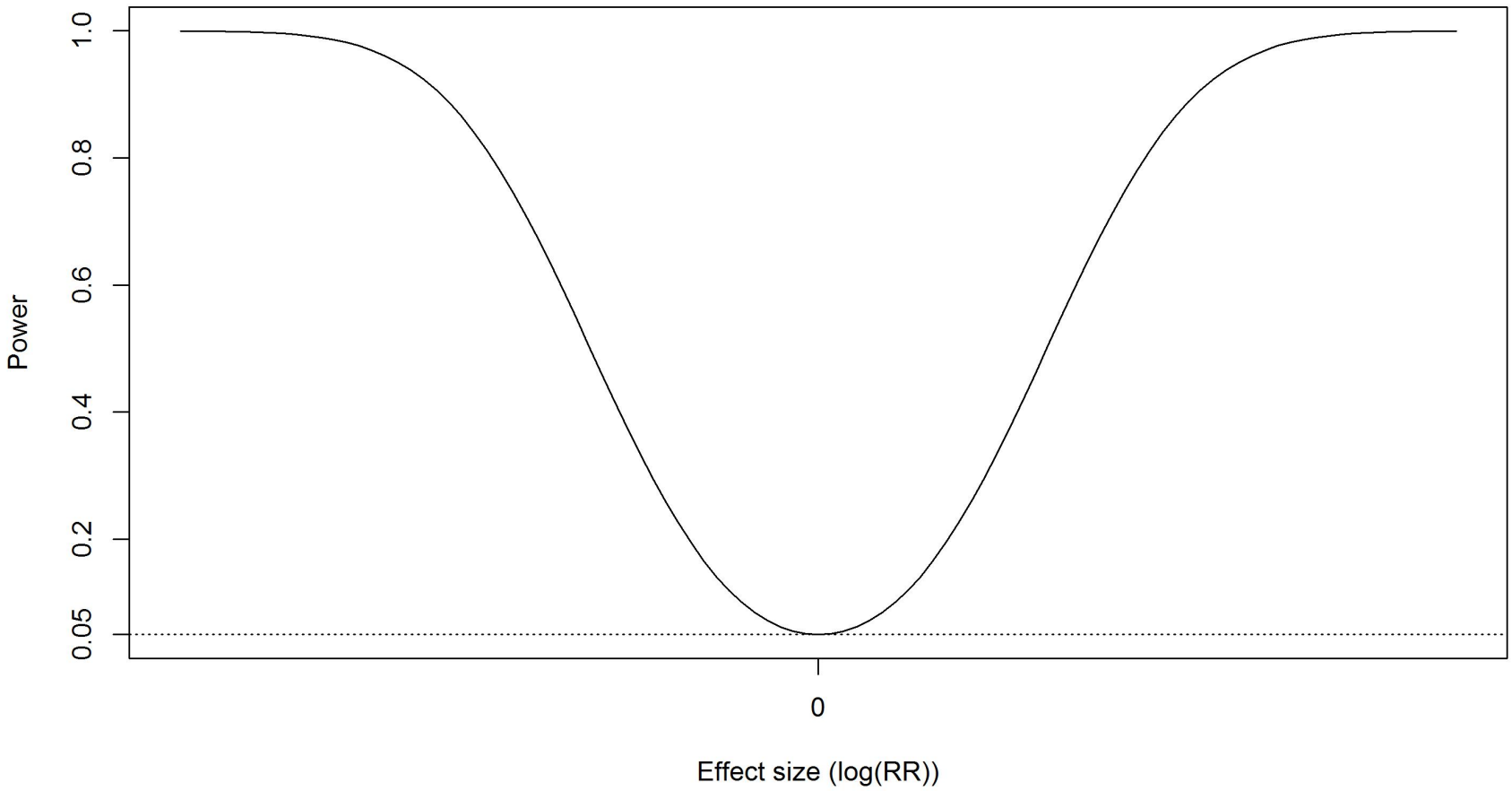
$$\Pi(\Delta) = 1 - \beta(\Delta).$$

  That is, the power of a test is the probability of rejecting H_0 for a given value of Δ
- Usually, the test is constructed so that $\Pi(\Delta) = 0.8$ for the smallest effect size considered clinically relevant

Error probabilities

		Decision	
		Fail to reject H_0	Reject H_0
Truth	H_0 is true	True negative $1 - \alpha$	False positive α
	H_0 is false	False negative β	True positive $1 - \beta$

Power function



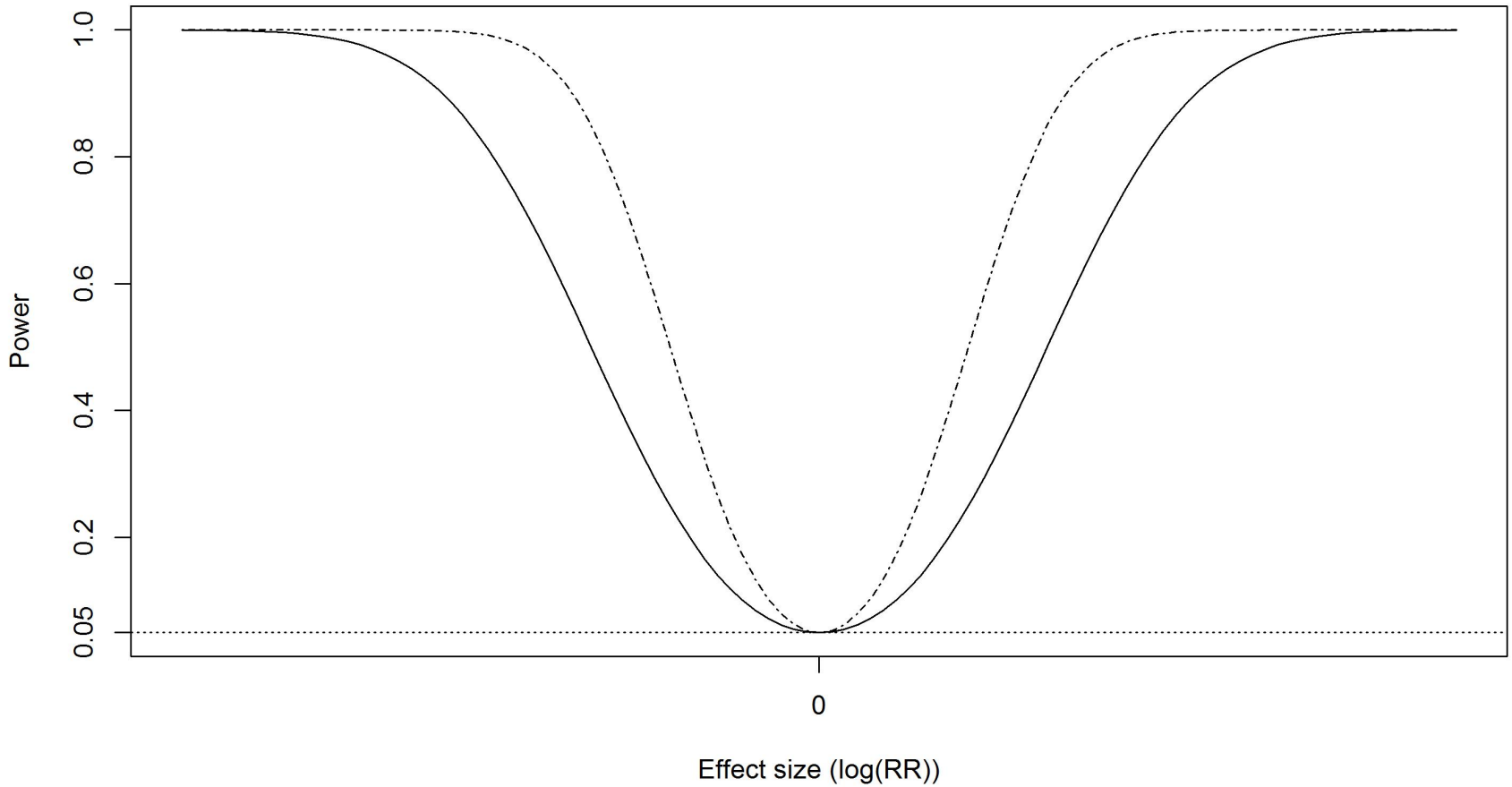
How to increase power?

How can we increase the statistical power?

- Increase significance level, α
- Increase detectable effect size, Δ
- Increase sample size/decrease standard error of parameter estimate

Power function–continued

Increase sample size



Poor statistical power

- Power affects the interpretation of results
- Poor power may result in a high number of false negatives
- Genetic association analyses are generally underpowered due to a large number of SNPs!!!

Issues of multiple testing in GWAS

Conventional significance level: $\alpha = 0.05$

Perform m tests, one for each SNP

Under H_0:

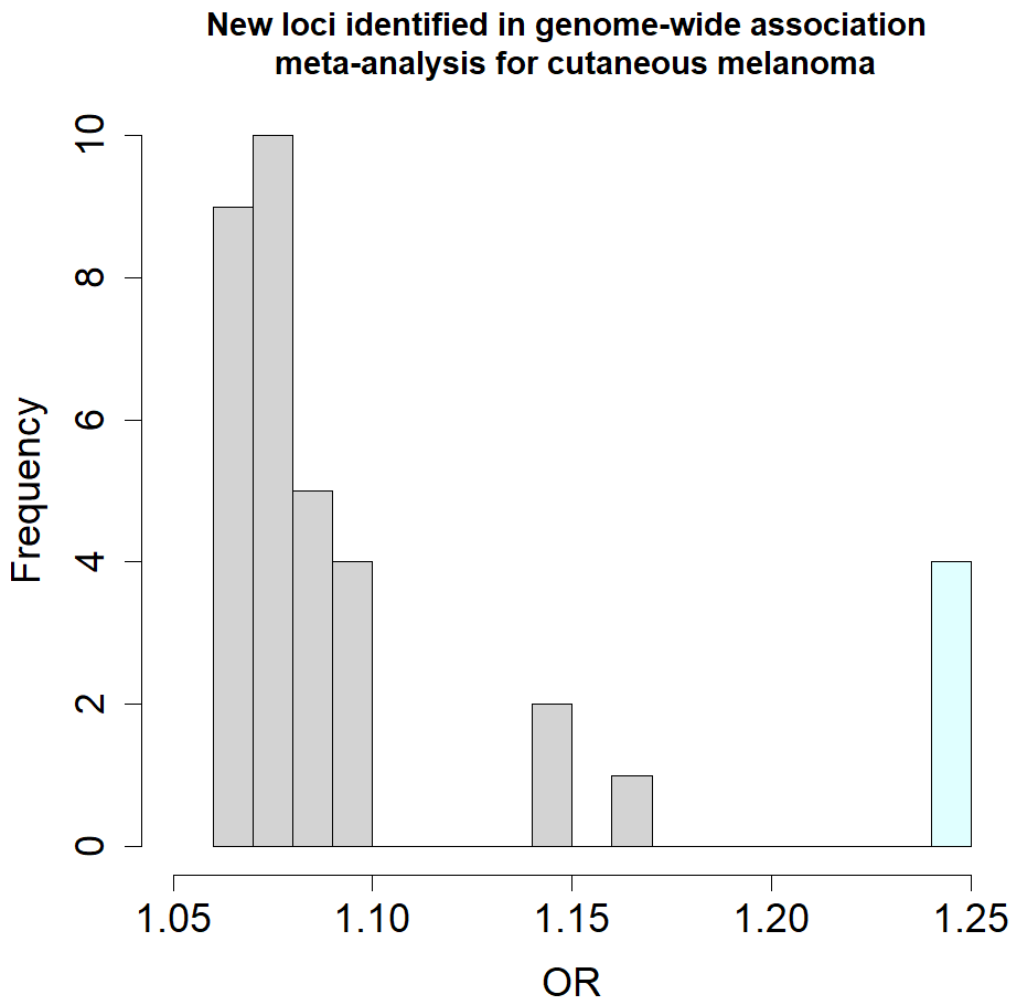
$m = 1{,}000{,}000$ SNPs

$$\Longrightarrow \text{ 50,000 false rejections by chance!}$$

Genome-wide (Bonferroni-corrected) significance threshold:

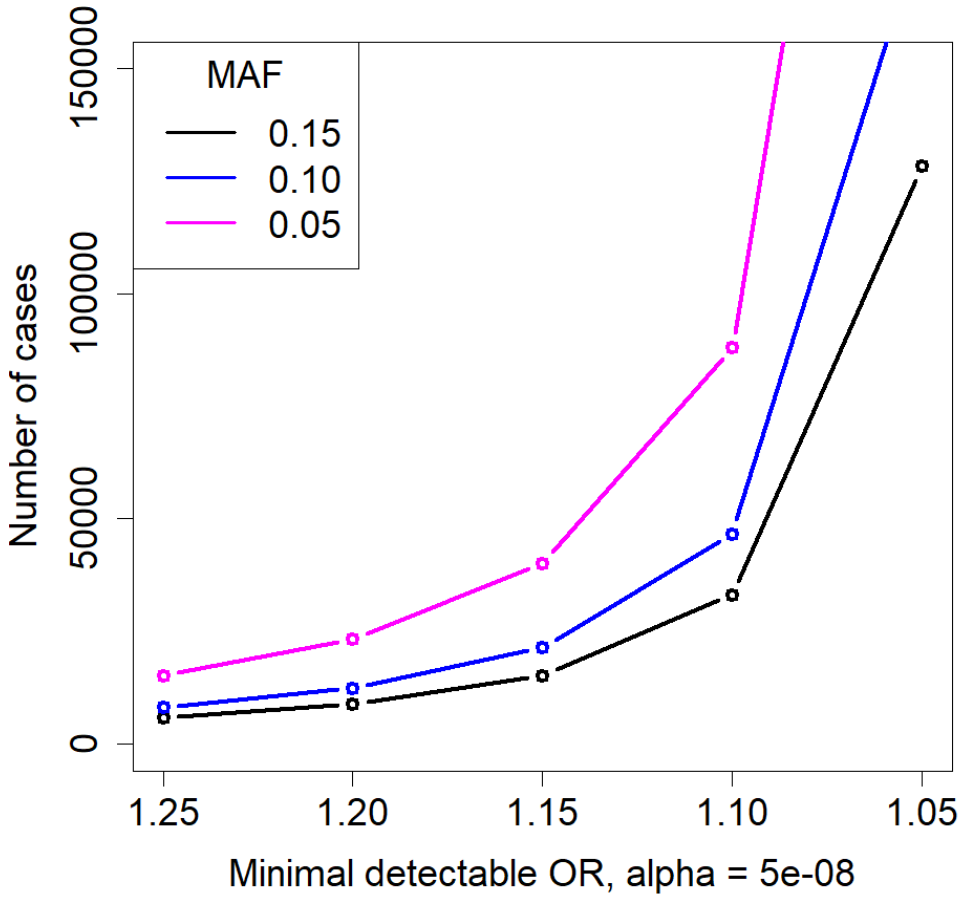
$$\alpha_{\text{Bonferroni}} = \alpha/m = 5 \times 10^{-8}$$

A typical range of identified effect sizes



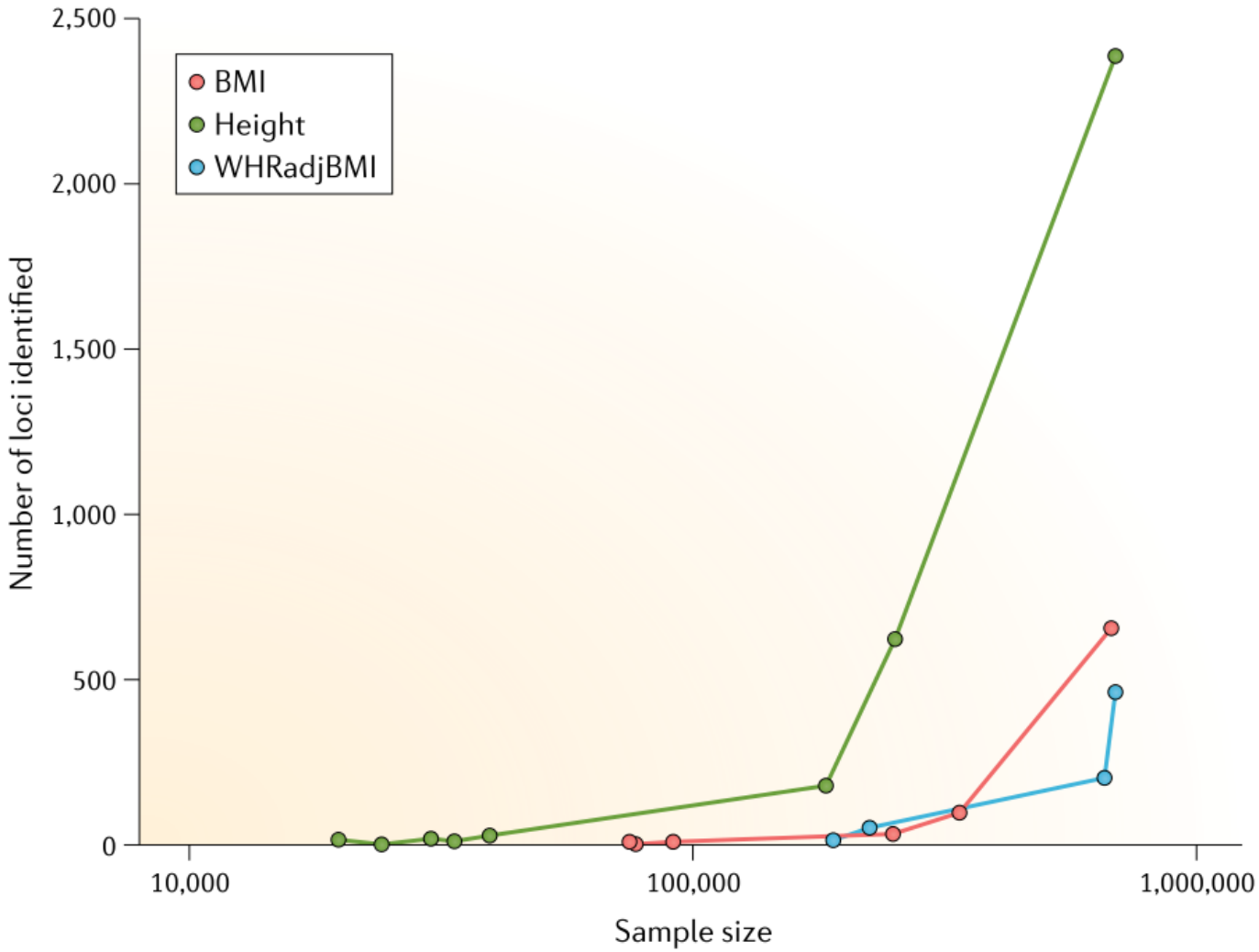
OR, Odds ratio
Numbers retrieved from Landi et al. *Nat Genet*. 2020;52:494–504.

Minimal detectable effect size



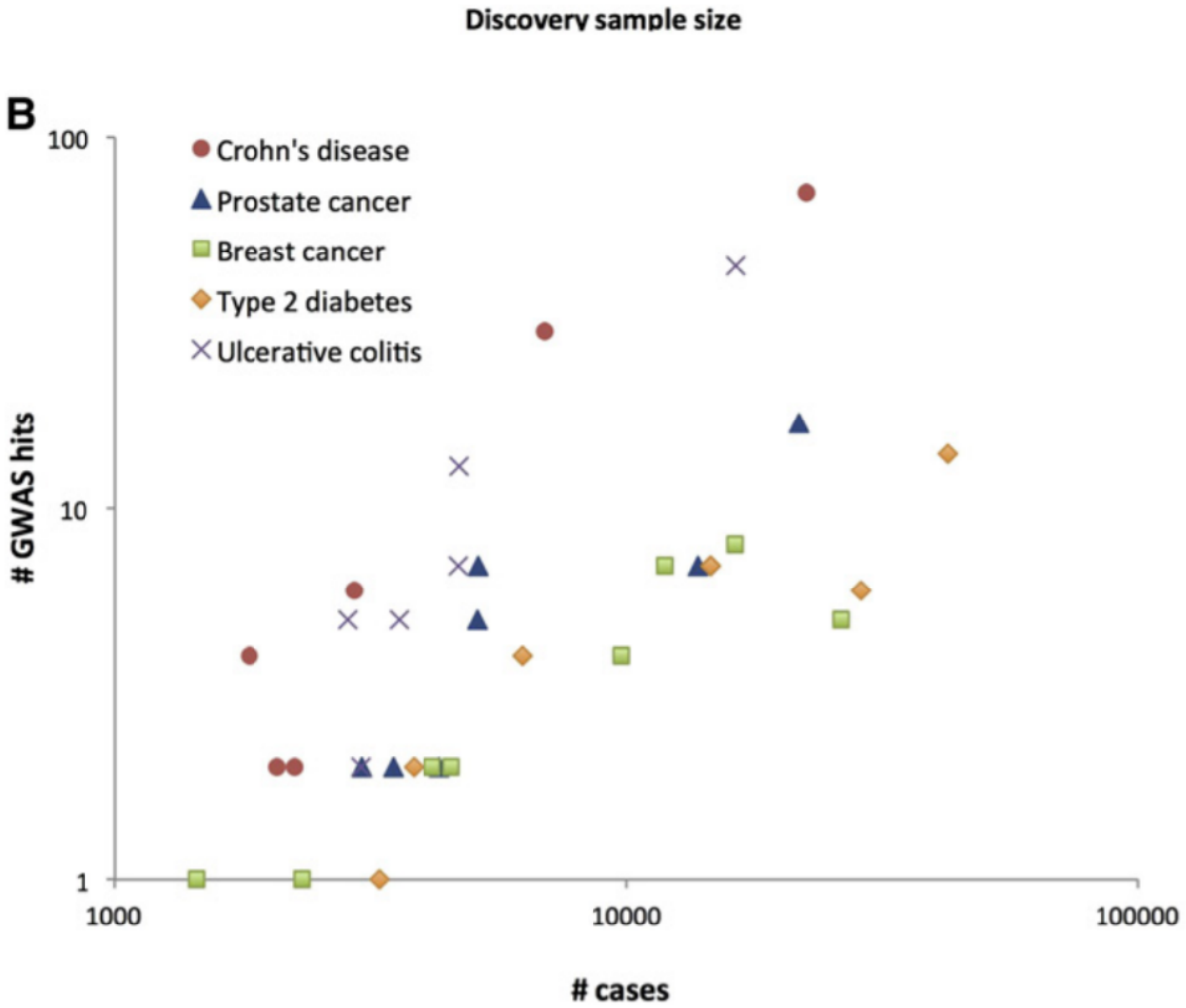
The number of cases in a case-control or a case-parent triad design needed to obtain 80% power. `snpSampleSize`,
https://people.uib.no/gjessing/genetics/software/haplin/
MAF, Minor allele frequency; OR, Odds ratio

Increasing the sample size



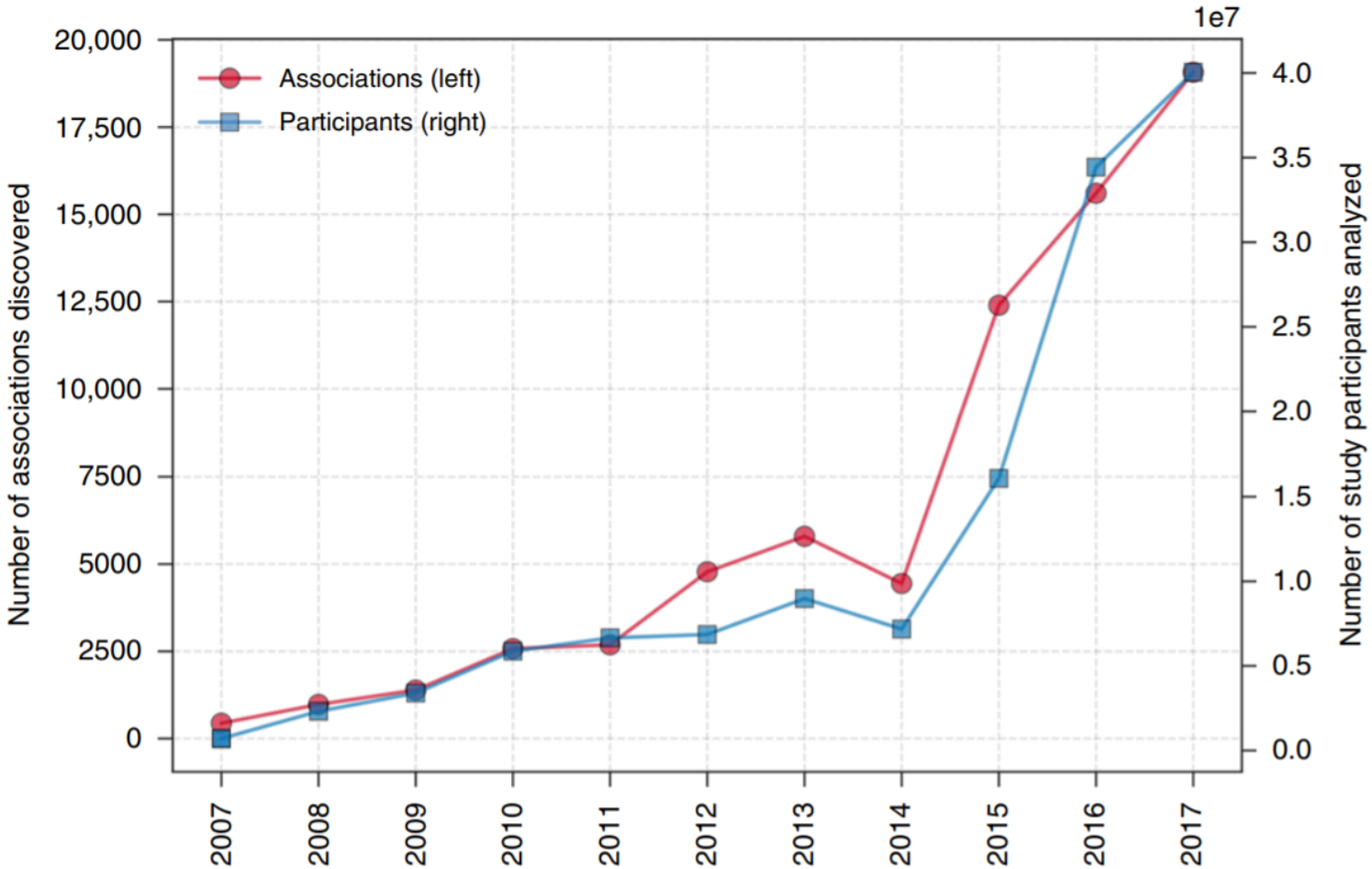
Tam et al. *Nat Rev Genet*. 2019;20:467–484.

Increasing the sample size



Visscher et al. *Am J Hum Genet*. 2012;90:7-24.

Increasing the sample size



Mills & Rahal. *Commun Biol*. 2019;2:9.

Sample size in genetic association studies

In genetic association analyses, the effective sample size depends on the number of families, allele/haplotype frequencies and family design

Sample size in genetic association studies/efficiency

```
snpPower(cases = list(c=100), controls = list(c=100),
        RR = 1.7, MAF = 0.2, alpha = 0.05)
```

cases.c	controls.c	RR	MAF	alpha	power
100	100	1.7	0.2	0.05	0.6178376

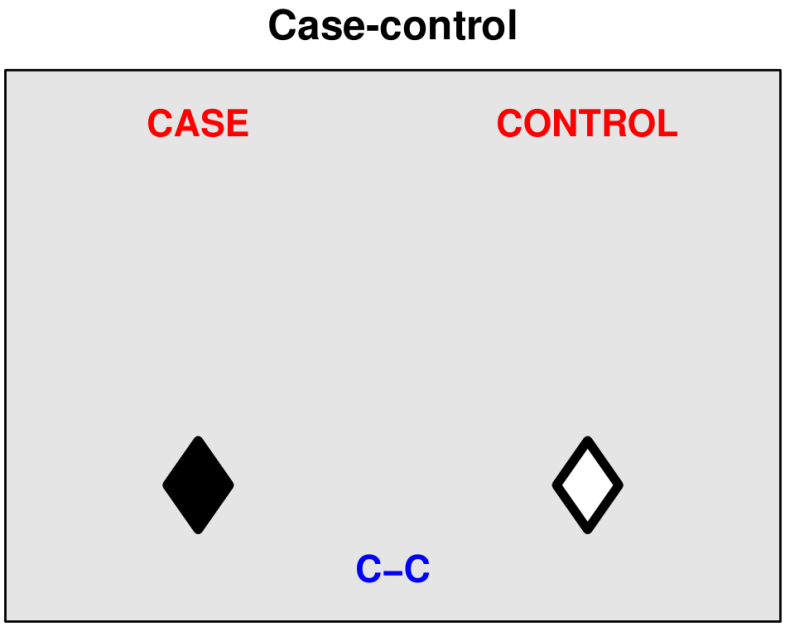
```
snpPower(cases = list(mfc=100), controls = list(mfc=0),
        RR = 1.7, MAF = 0.2, alpha = 0.05)
```

cases.mfc	controls.mfc	RR	MAF	alpha	power
100	0	1.7	0.2	0.05	0.6178376

Sample size in genetic association studies/efficiency

Analyzing a diallelic SNP using 100 case children and 100 control children

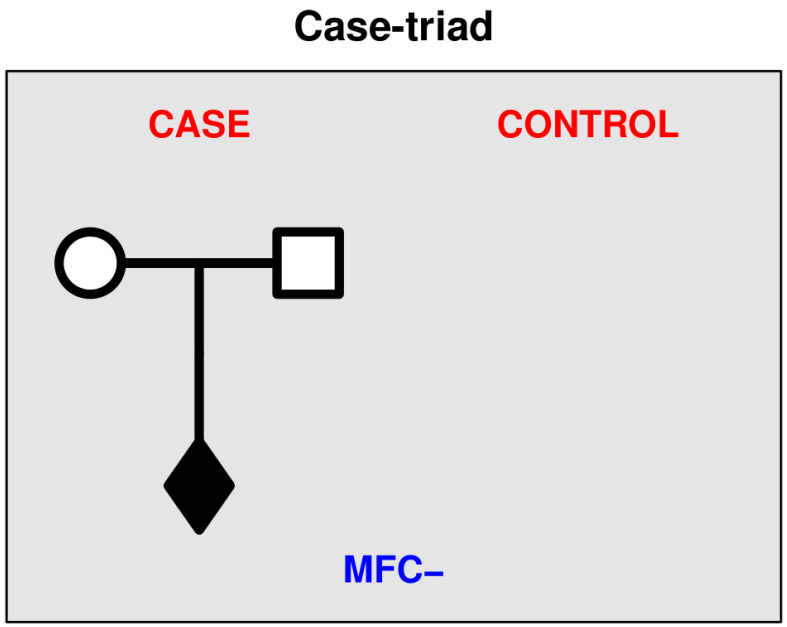
- 200 case alleles and 200 control alleles
- Genotyping cost: 200 individuals



Sample size in genetic association studies/efficiency

Analyzing a diallelic SNP using 100 case-triads

- 200 case alleles, 200 control alleles
- Genotyping cost: 300 individuals



Which design is more efficient?

Power calculations in Haplin–fetal effects

```
snpPower(cases = list(c=100), controls = list(c=100),
        RR = 1.7, MAF = 0.2, alpha = 0.05)
```

```
snpPower(cases = list(mfc=100), controls = list(mfc=0),
        RR = 1.7, MAF = 0.2, alpha = 0.05)
```

```
snpPower(cases = list(mfc=100), controls = list(mfc=100),
        RR = 1.7, MAF = 0.2, alpha = 0.05)
```

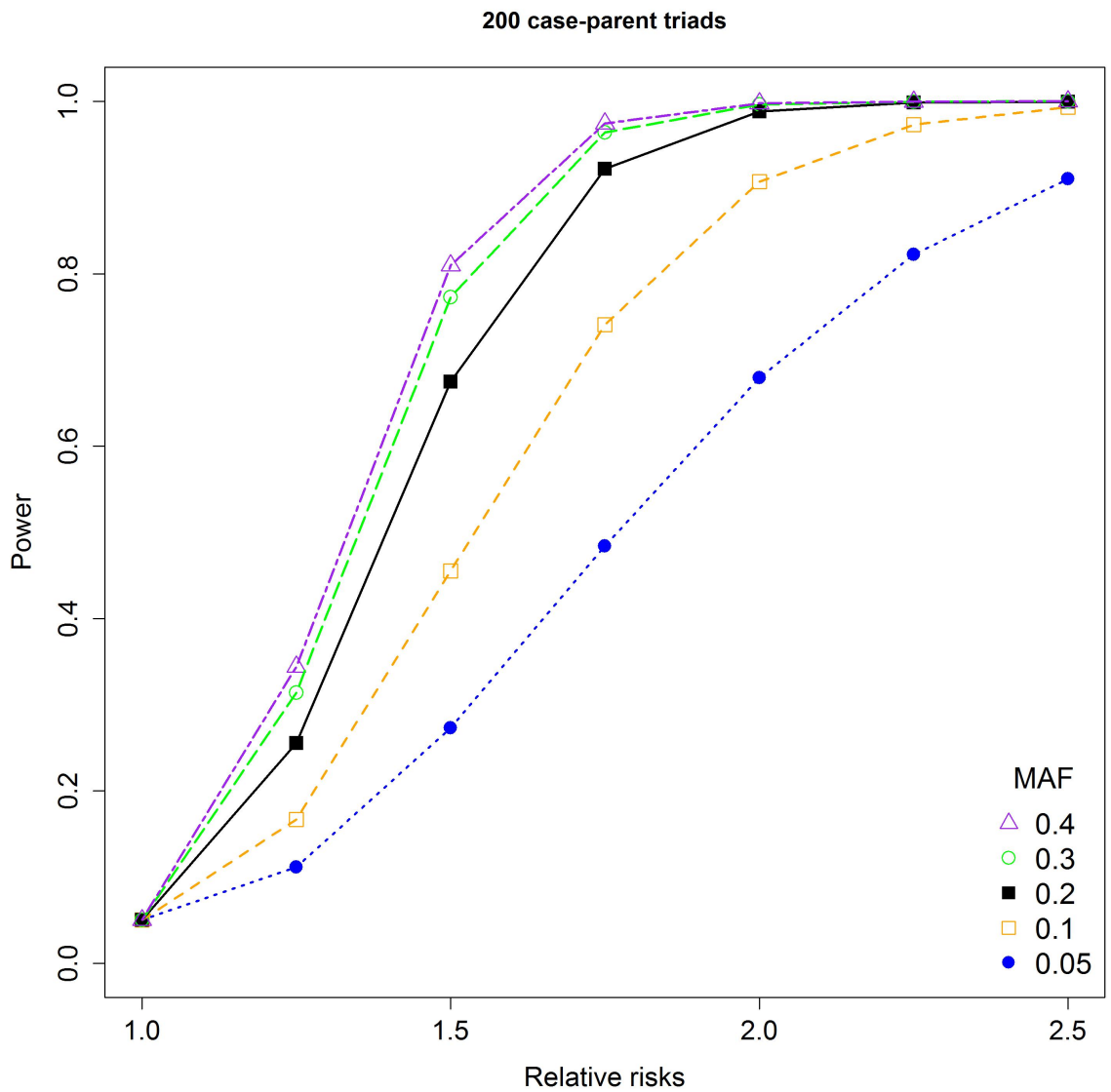
Sample size calculations in Haplin–fetal effects

```
snpSampleSize(fam.cases = "mfc",
        fam.controls = "no_controls", RR = 1.1,
        MAF = 0.1, alpha = 0.05, power = 0.8)
```

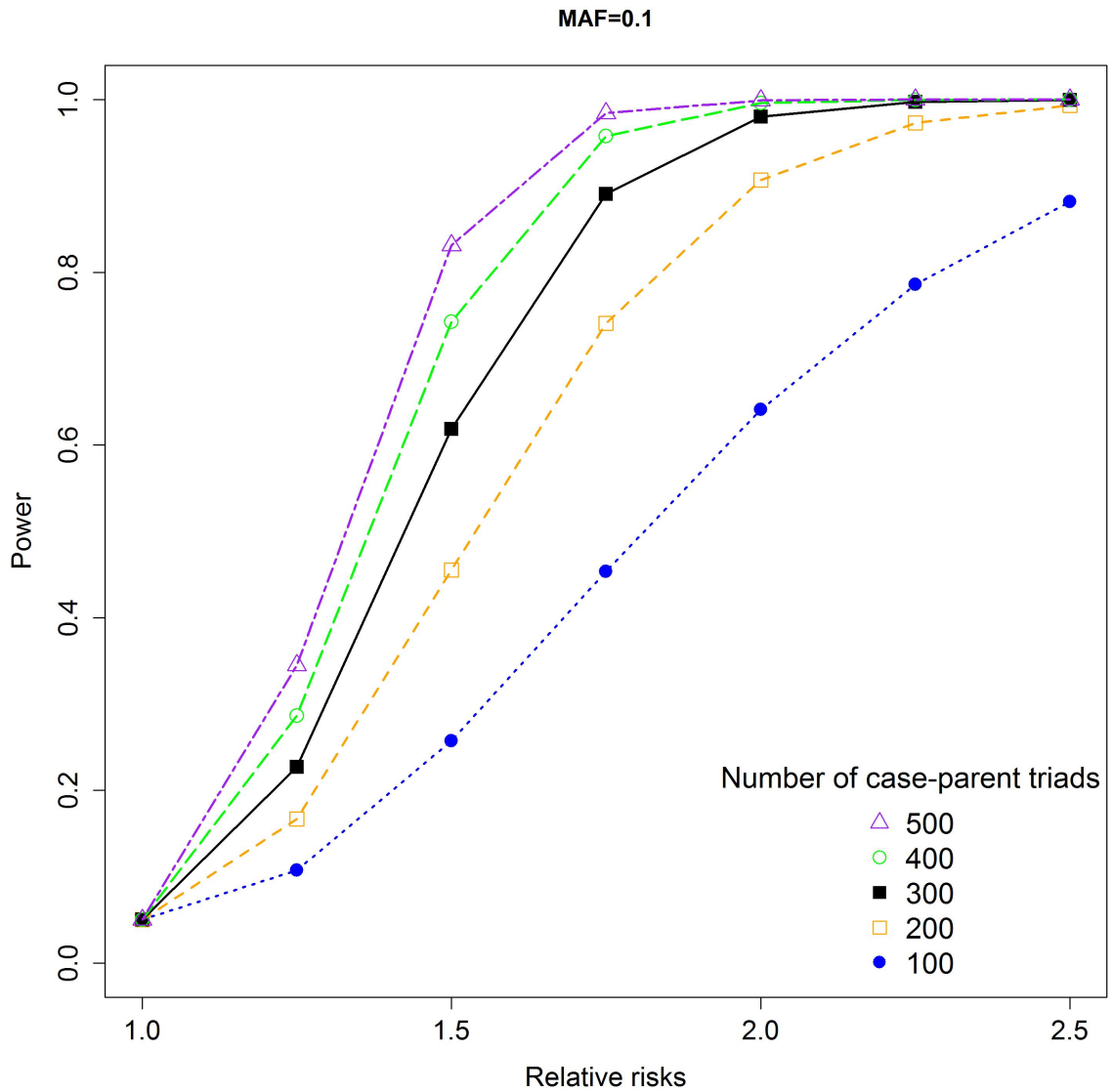
```
snpSampleSize(fam.cases = "mfc",
        fam.controls = "no_controls", RR = 1.5,
        MAF = 0.1, alpha = 0.05, power = 0.8)
```

```
snpSampleSize(fam.cases = "mfc",
        fam.controls = "no_controls", RR = 1.5,
        MAF = 0.15, alpha = 0.05, power = 0.8)
```

Power function–fetal effects



Power function–fetal effects



Power calculations through asymptotic approximations

Fetal effects

```
hapPowerAsymp(cases = c(mfc=100),
    controls = c(mfc=100),
    haplo.freq = c(0.2,0.8), RR = c(1.7,1))
```

Power calculations asymptotic approximations

Parent-of-origin (PoO) effects

```
hapPowerAsymp(cases = c(mfc=200),
    controls = c(mfc=200), haplo.freq = c(0.2,0.8),
    RRcm = c(1.7,1), RRcf = c(1,1))
```

NB! Remember that the PoO effect is defined by RRcm/RRcf

Power calculations asymptotic approximations

Gene-environment interactions

```
hapPowerAsymp(n.strata = 2,
              cases = list(c(mfc=150),c(mfc=300)),
              controls = c(mfc=300),
              haplo.freq = c(0.1,0.9),
              RR = list(c(2,1),c(1,1)))
```

Power calculations through simulations

Fetal effects

```
res.hapRun <- hapRun(nall = c(2), cases = c(mfc=100),
              controls = c(mfc=100),
              haplo.freq = c(0.2,0.8), RR = c(1.7,1),
              RRstar = c(1,1), hapfunc = "haplin",
              response = "mult", n.sim = 200)

hapPower(res.hapRun)
```

Power calculations through simulations

Parent-of-origin effects

```
res.hapRun <- hapRun(nall = c(2), cases = c(mfc=200),
              controls = c(mfc=200), haplo.freq = c(0.2,0.8),
              RRcm = c(1.7,1), RRcf = c(1,1), RRstar = c(1,1),
              hapfunc = "haplin", poo = T,
              response = "mult", n.sim = 200)

hapPower(res.hapRun)
```

Power calculations through simulations

Gene-environment interaction

```
res.hapRun <- hapRun(nall = c(2), n.strata = 2,
              cases = list(c(mfc=150),c(mfc=300)),
              controls = c(mfc=300),
              haplo.freq = c(0.1,0.9),
              RR = list(c(2,1),c(1,1)), RRstar = c(1,1),
              hapfunc = "haplinStrat",
              response = "mult", n.sim = 200)

hapPower(res.hapRun)
```