GWAS Meta-Analysis

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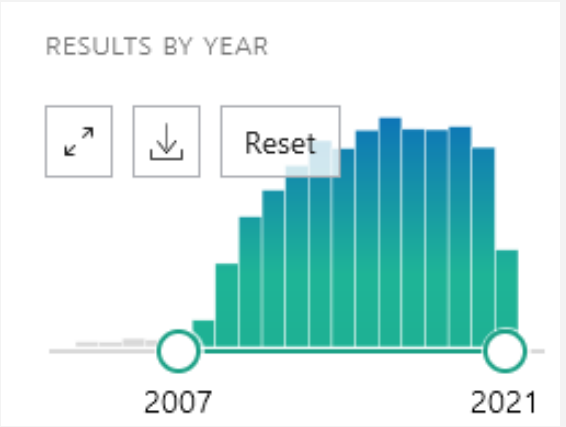
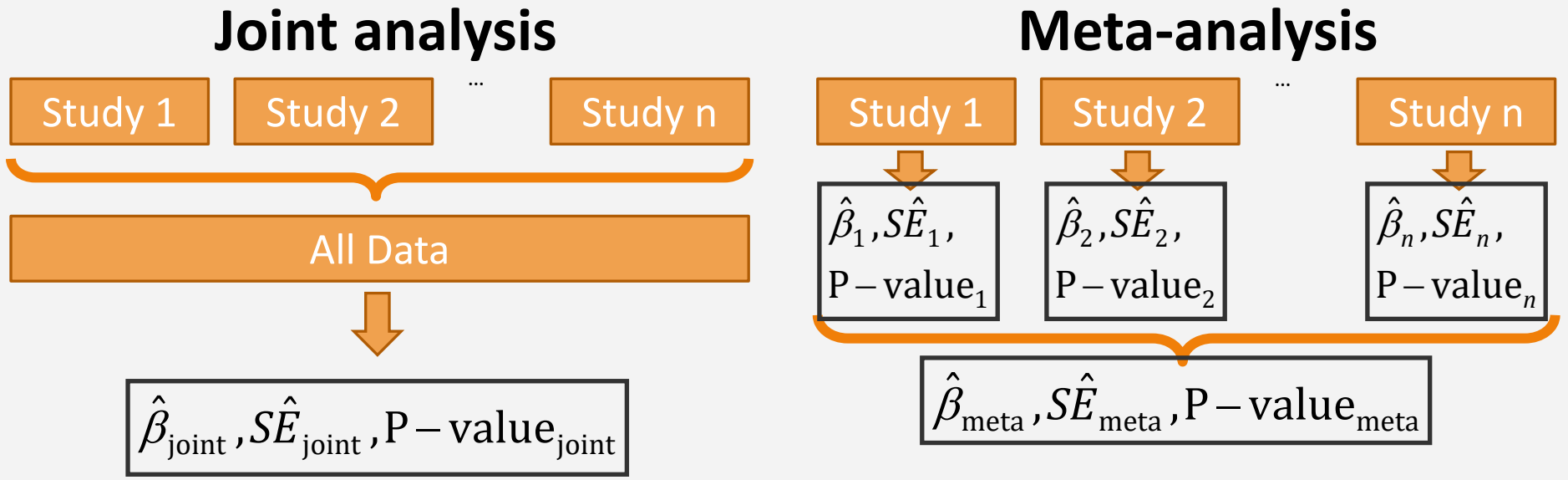
The 2021 Virtual Workshop on Statistical Genetic Methods for Human Complex Traits

Combining data across studies

- Aims:
  - Estimate the overall, or combined effect
  - Explore differences between cohorts – heterogeneity
  - Improve power
  - Replicate effects



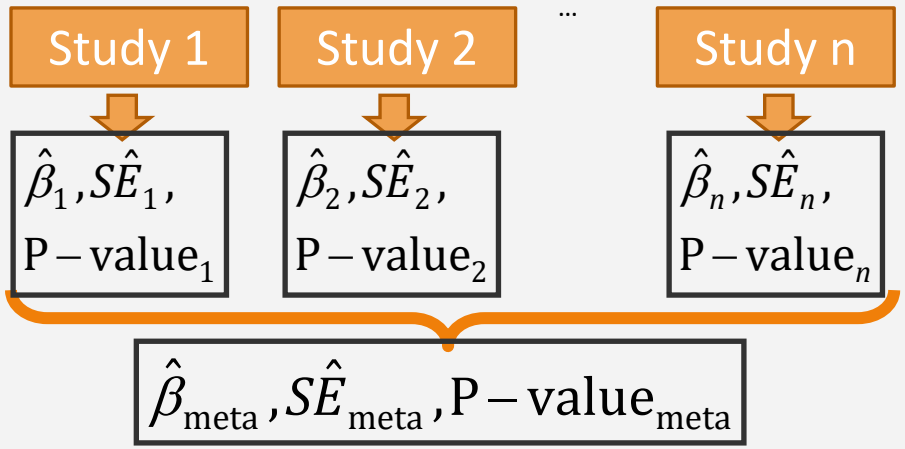
Joint vs Meta-analysis



For common variants, joint and meta-analysis have similar power (Lin & Zeng, *Genet. Epidemiol.*, 2010)

How we use meta-analysis in GWAS

- Commissioned analyses rather than MA of previously published findings
  - Analysis protocol
    - Imputation reference
    - Phenotypic definition
    - Covariates to be included
    - Population stratification
    - Analyses to be run
    - Output format



Types of meta-analysis – Fixed Effect

- Each SNP has a “true effect size” on the trait.
- This effect is shared by all cohorts.
- The observed effect sizes in the different cohorts will be distributed around the “true effect size” with a variance that depends on the precision of the different cohorts

Types of meta-analysis – Fixed Effect

- We weight each cohorts effect size by it's precision
- Error in our estimate is due to random error within studies
- The combined effect = the meta-analytic estimate

Types of meta-analysis – Random Effect

- The true effect for a SNP varies between cohorts.
- The studies included in the meta-analysis are assumed to be a random sample reflecting the distribution of true effects

Types of meta-analysis – Random Effect

- Error in our estimate is due to random error within AND between studies
- Weights reflect these two sources of error and are less dependent on sample size
- The mean effect in this distribution = the meta-analytic estimate

Types of meta-analysis – Random Effect

- Traditionally, null hypothesis for RE model is that the mean of the effects is 0
  - lower power than FE
- Correct null hypothesis for GWAS is that all effects are 0
  - Modification proposed by Han & Eskin 2011 tests the null hypothesis of exactly 0 effect in every study – RE2
  - Implemented in Meta (webpage no longer works)

Types of meta-analysis – Others

- Bayesian partition model
  - Cohorts are grouped into clusters. Effect is assumed be the same within but different between clusters.
  - MANTRA (Meta-ANalysis of Transethnic Association studies) - Andrew Morris - Genet Epidemiol. 2011; 35(8): 809–822. PMCID: PMC3460225

Types of meta-analysis – Others

- Multivariate GWAS packages
  - MTAG and GenomicSEM – next week
- Continuous & Binary meta-analysis
  - Demontis, Walters et al Nat Genet. 2019; 51(1): 63–75. PMCID: PMC6481311 (Sup information)

Setting up a meta-analysis

- Start with an analysis plan
  - Decide on QC of input and analytic approach
  - Define your primary analyses
  - Define any secondary analyses – sensitivity, populations
  - Map out intended follow-ups
  - Define replication
  - Preregistration or public posting is strongly encouraged
  - Allow a lot more time than you think you will need

Software for running meta-analysis

- Important considerations
  - Types of analyses the program can run
  - QC requirements
  - Strand flipping
    - Allele frequency tracking
  - What you want to do your output
    - Genomic control vs LDscore regression
    - Beta & SE vs Z

Software for running meta-analysis

- Software
  - METAL
  - ? GWAMA (Magi & Morris)
  - ? Meta(Han & Eskin)
  - R & Stata packages

QC of cohort level data

- Variant naming
- Allele Frequency - MAF .5 or 1%
- Imputation accuracy (r^2) - Typically .6 (.8 if hard calls were analysed)
- Plots - Manhattan, QQ, P-Z
- MAF compared to reference - Strand
- Lambda calculation - Checking for confounding
- Packages are available to help with this i.e. EasyQC

Choosing an analytic approach

- Metal
  - Fixed effect analysis – Inverse variance weighted
    - Requires: beta, SE, alleles
    - Outputs: beta, SE, p, N, heterogeneity, MAF

	Inverse variance based
Inputs	β_i- effect size estimate for study *i*
	se_i - standard error for study *i*
Intermediate Statistics	$w_i = 1/SE_i^2$
	$se = \sqrt{1/\sum_i w_i}$
	$\beta = \sum_i \beta_i w_i / \sum_i w_i$
Overall *Z*-Score	$Z = \beta / SE$
Overall *P*-value	

Choosing an analytic approach

- Metal
  - Fixed effect analysis – Sample size weighted
    - Requires: direction, P, N , alleles
    - Outputs: Z, p, N, heterogeneity, MAF
    - Sample overlap correction

	Sample size based
Inputs	N_i - sample size for study i
	P_i–P-value for study i
	Δ_i - direction of effect for study i
Intermediate Statistics	$Z_i = \Phi^{-1}(P_i/2) * \text{sign}(\Delta_i)$
	$w_i = \sqrt{N_i}$
Overall Z-Score	$Z = \frac{\sum_i Z_i w_i}{\sqrt{\sum_i w_i^2}}$
Overall P-value	$P=2\Phi(\lvert -Z \rvert)$

Choosing an analytic approach

- Random Metal
  - Requires: beta, SE, p, N, alleles
  - Outputs: Both FE and RE results beta, SE, p, heterogeneity, tau^2

Why would you chose N weighted or RE?

- Inverse variance FE meta-analysis are sensitive to deviations in scaling between studies
- N weighted FE meta-analyses are less sensitive to this
- RE meta-analyses are more appropriate for situations where the effect size differs between cohorts

Questions?