

# LDL Meta-analysis

SMED 8020

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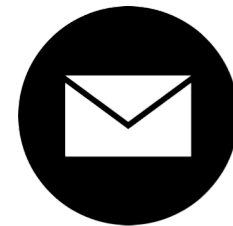
PhD Candidate



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<https://github.com/bnwolford>



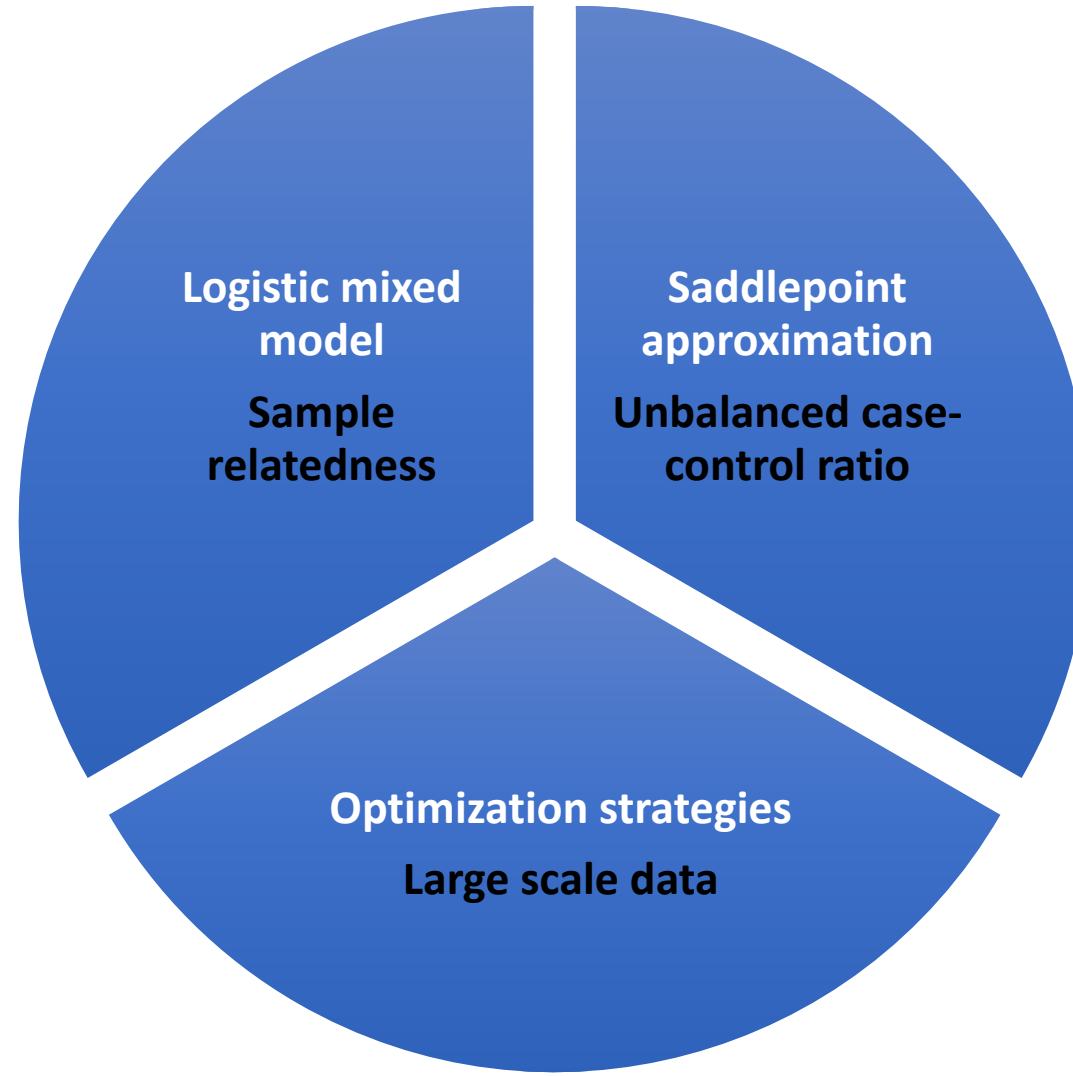
[bwolford@umich.edu](mailto:bwolford@umich.edu)

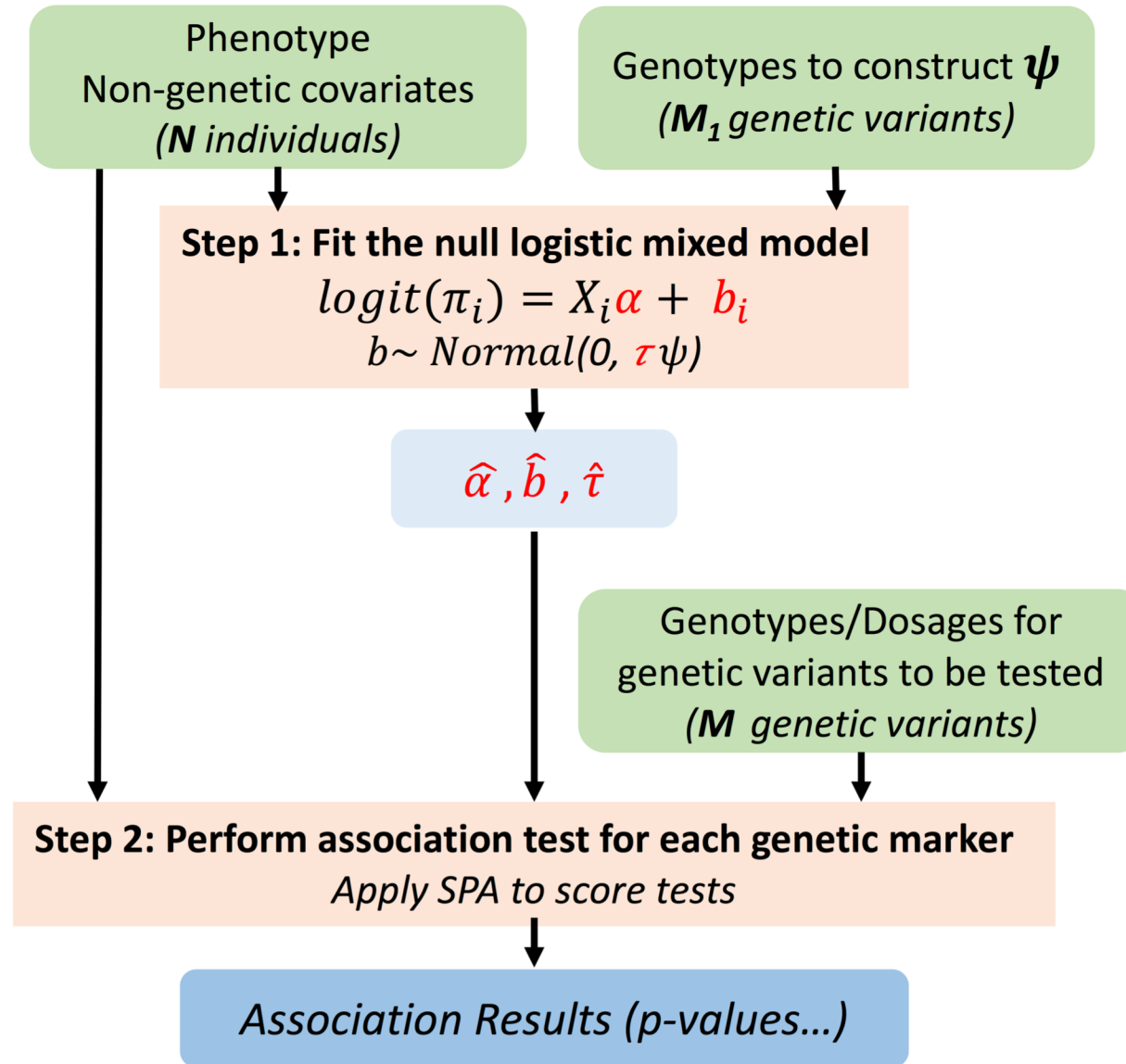
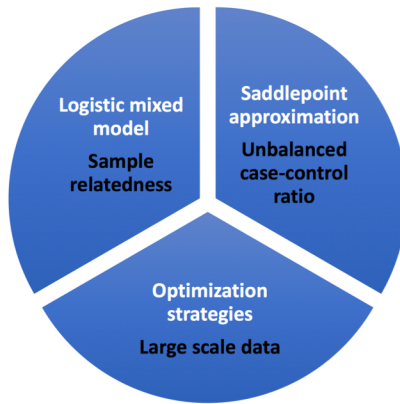
# In choosing software for GWAS consider...

- Is your trait binary or quantitative?
  - Logistic vs linear regression
- Is your sample size large and what computational capability do you have?
  - Memory and time constraints
- Is your sample related?
  - Subjects are not independent
- Is your sample geographically/ancestrally homogeneous?
  - Population stratification

# SAIGE

Scalable and Accurate Implementation of  
GEneralized mixed model





# Meta-Analysis

- Alleviates concerns regarding privacy of study participants because works on summary statistics instead of individual level data
- Increase statistical power by increasing sample size
  - As efficient as pooling individual level data
- Analyze different ancestries separately before combining to avoid population stratification

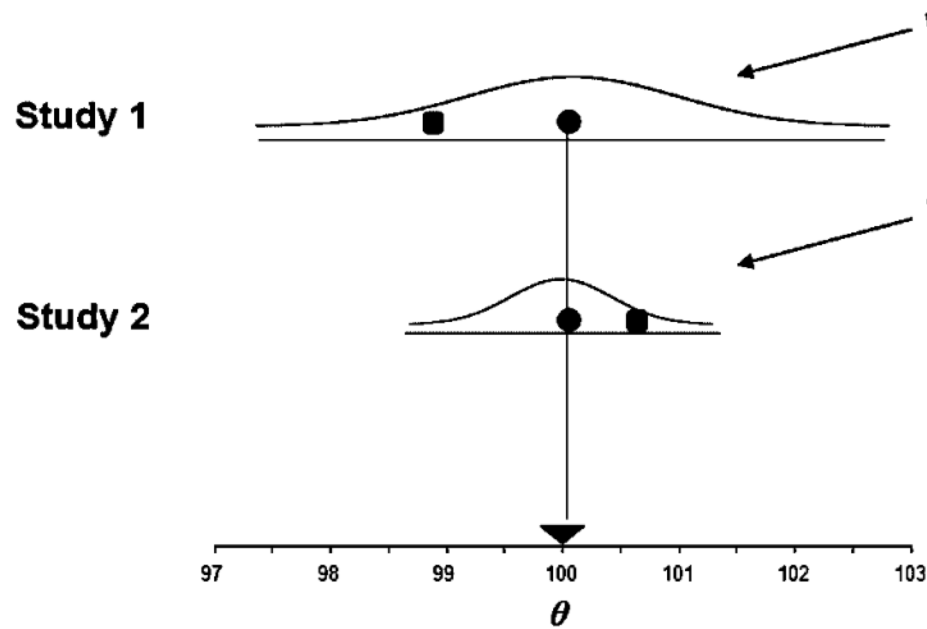
# Assumptions

- Each sub-study has controlled type 1 error and proper QC
- No sample overlap between studies
  - Methods in development for this situation  
([https://genome.sph.umich.edu/w/images/7/7b/METAL\\_sample\\_overlap\\_method\\_2017-11-15.pdf](https://genome.sph.umich.edu/w/images/7/7b/METAL_sample_overlap_method_2017-11-15.pdf))
- Fixed or random effects meta-analysis have their own assumptions
- Estimated beta value is in terms of the same allele, consistent direction

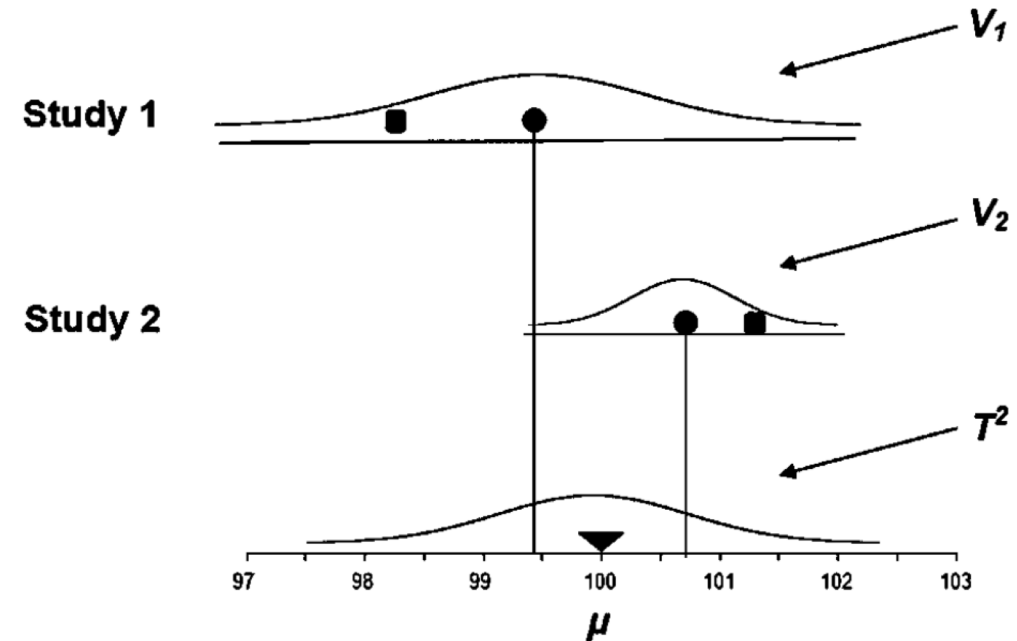
# Random vs Fixed effects

Fixed: one true effect size that underlies all the studies in the analysis

Random: distribution of true effect sizes, effect size in each study is different with means assumed to be chosen from Gaussian



## Fixed effects



## Random effects

**Table 1.** Formulae for meta-analysis

	Analytical strategy	
	Sample size based	Inverse variance based
Inputs	$N_i$ - sample size for study $i$ $P_i$ - $P$ -value for study $i$ $\Delta_i$ - direction of effect for study $i$	$\beta_i$ - effect size estimate for study $i$ $se_i$ - standard error for study $i$
Intermediate Statistics	$Z_i = \Phi^{-1}\left(1 - \frac{p_i}{2}\right) * \text{sign}(\Delta_i)$ $w_i = \sqrt{N_i}$	$w_i = 1/SE_i^2$ $se = \sqrt{1/\sum_i w_i}$ $\beta = \sum_i \beta_i w_i / \sum_i w_i$
Overall Z-Score	$Z = \frac{\sum_i Z_i w_i}{\sqrt{\sum_i w_i^2}}$	$Z = \beta/SE$
Overall $P$ -value	$P = 2\Phi( -Z )$	



# Other GWAS meta-analysis software

- GWAMA (Genome-Wide Association Analysis)
- METASOFT
- MANTRA (Meta-Analysis of Trans-ethnic Association Studies)
- MR-MEGA (Meta-Regression of Multi-Ethnic Genetic Association)