Phenotype Harmonization in Association Studies

slides from Adrienne Stilp and Leslie Emery

Phenotype harmonization is a specific case of data harmonization

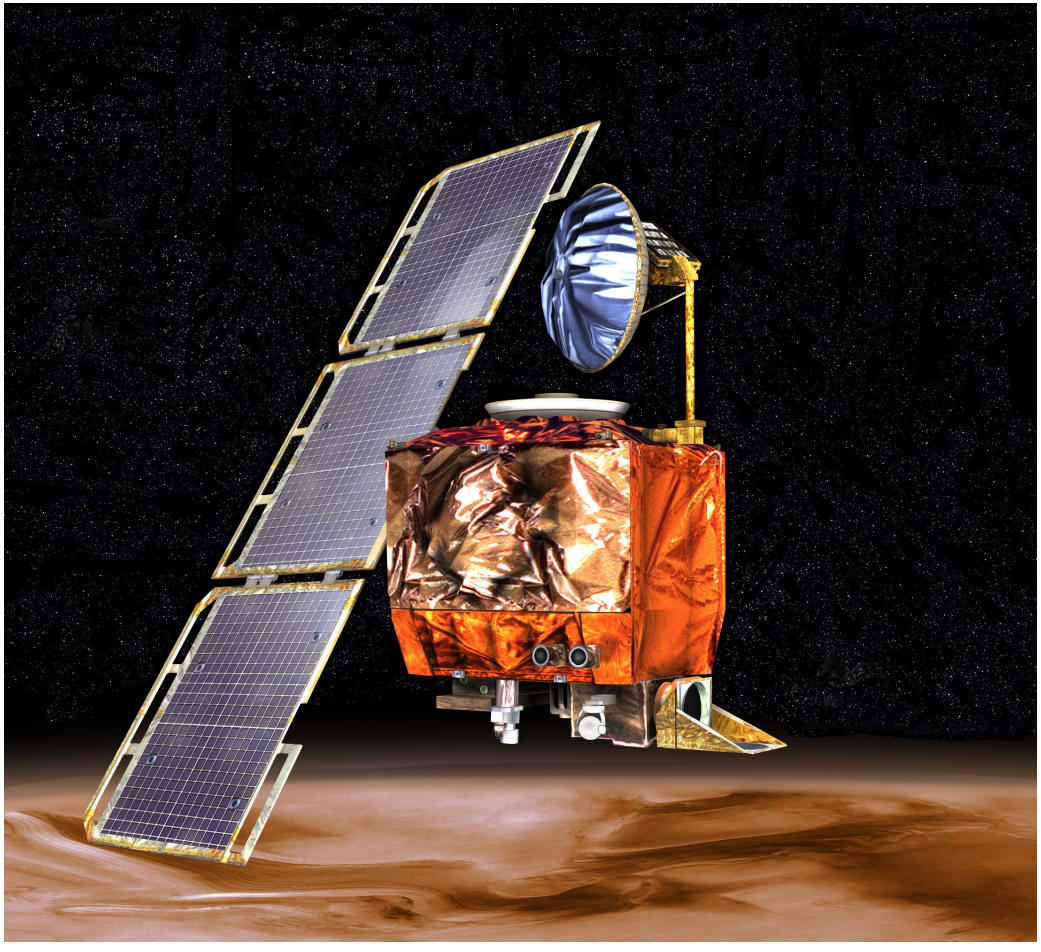
> *Data harmonization refers to all efforts to combine data from different sources and provide users with a comparable view of data from different studies. This process is becoming more and more significant in demography and sociology research, since the needs of data harmonization is rapidly growing as the volume and the need to share existing data explodes.*

– Data Sharing for Demographic Research, University of Michigan

Do we really need to worry about harmonizing data?

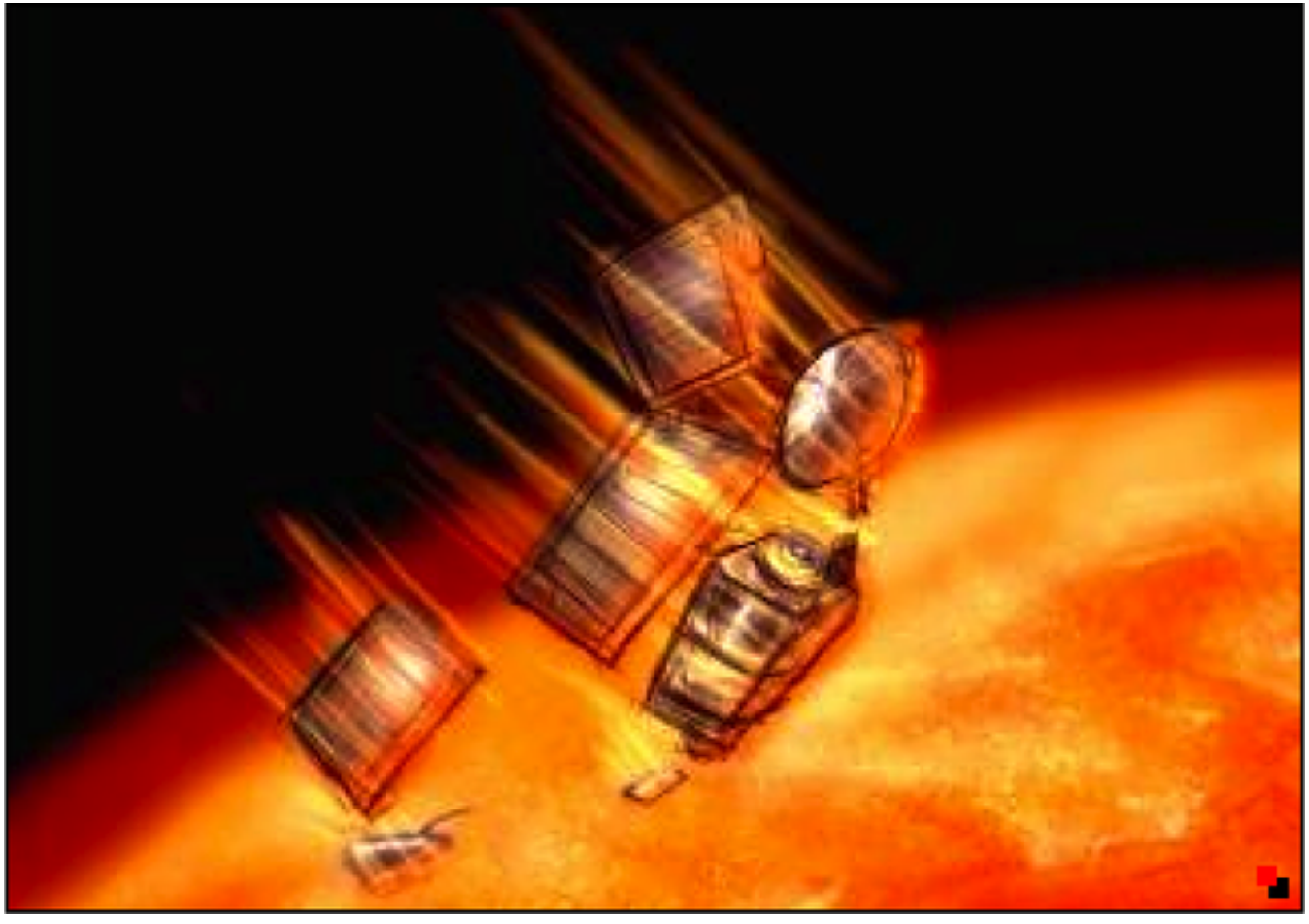
There is **much more** to data harmonization than just renaming variables and combining files together!

The Mars Climate Orbiter



NASA/JPL/Corby Waste

Lack of data harmonization can be disastrous!



More details from Wikipedia

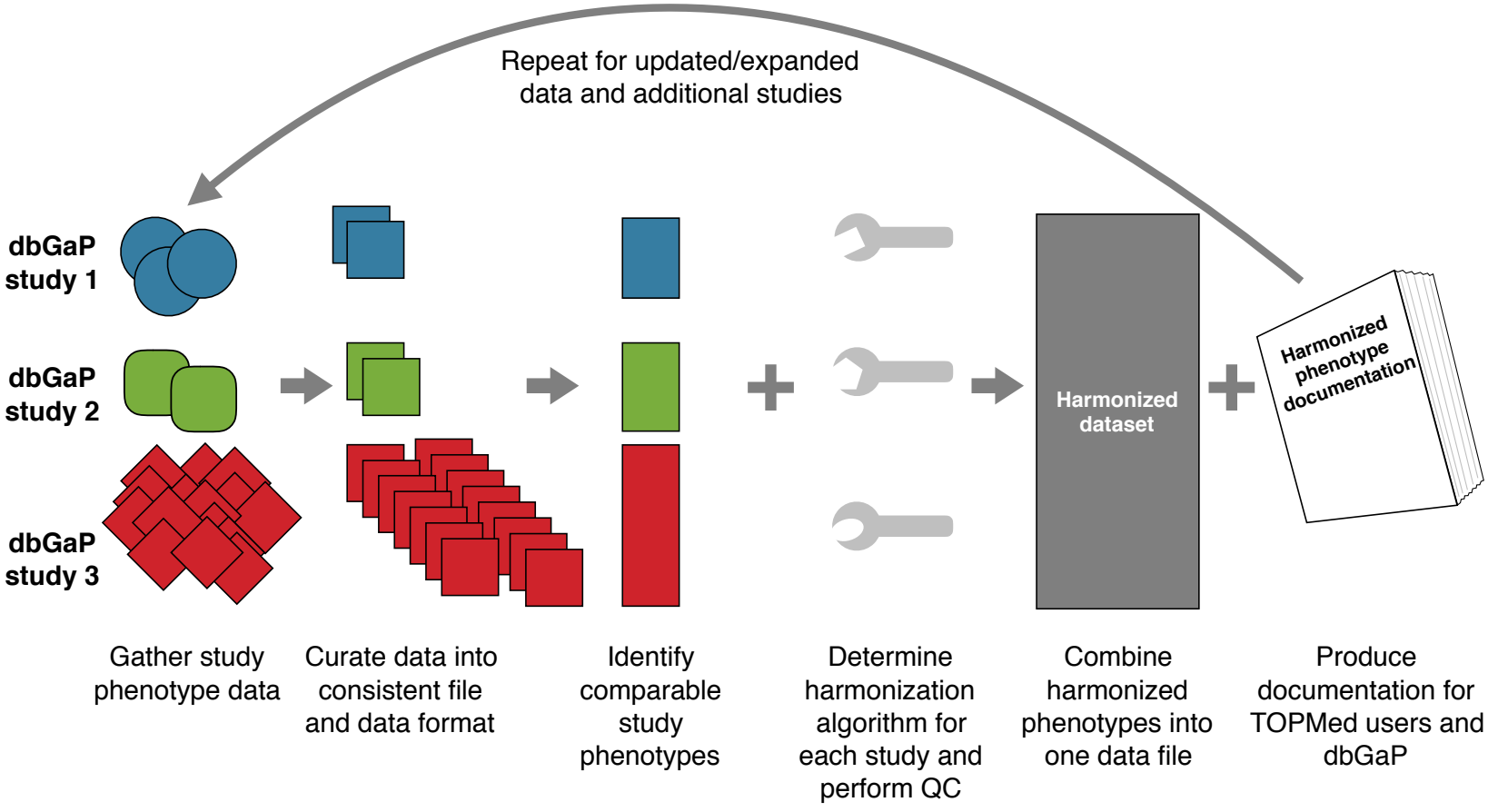
What is phenotype harmonization?

Phenotype harmonization is the process by which source phenotype variables from different studies are transformed so that they can be analyzed together.

Phenotype harmonization is a major undertaking in large projects that combine pre-existing studies. Examples include:

- NHLBI GO Exome Sequencing Project
- CHARGE Consortium (Cohorts for Heart & Aging Research in Genomic Epidemiology)
- TOPMed (Trans Omics for Precision Medicine)

Harmonizing phenotypes from many studies in TOPMed



Working with phenotype data has unique challenges

- Genotypes
  - Big but **homogeneous**
  - Similar across studies – automated processing
- Phenotypes
  - Small but **heterogeneous**
  - Every study collects data differently – manual effort required
- Too much noise can cause a loss of power and mask true associations.

What needs to be done in phenotype harmonization?

1. Define the target harmonized phenotype
2. Decide which studies can be included
3. Process source phenotype data by study
   - Perform QC
   - Determine harmonization algorithm
   - Once per study
4. Estimate quality of harmonized phenotype output
   - More QC
   - May need to repeat previous steps
5. Document and disseminate harmonized phenotypes

Documentation

Your harmonized phenotype data should be reproducible.

- Accurate reporting in papers
- Able to add new studies in the future

What do you need?

- Definition of the harmonized phenotype
- Which component source phenotypes were used
  - Source file?
  - Version?
- What algorithms were used
  - Ideally, the exact code you used
- How QC issues were addressed

QC of study source phenotypes

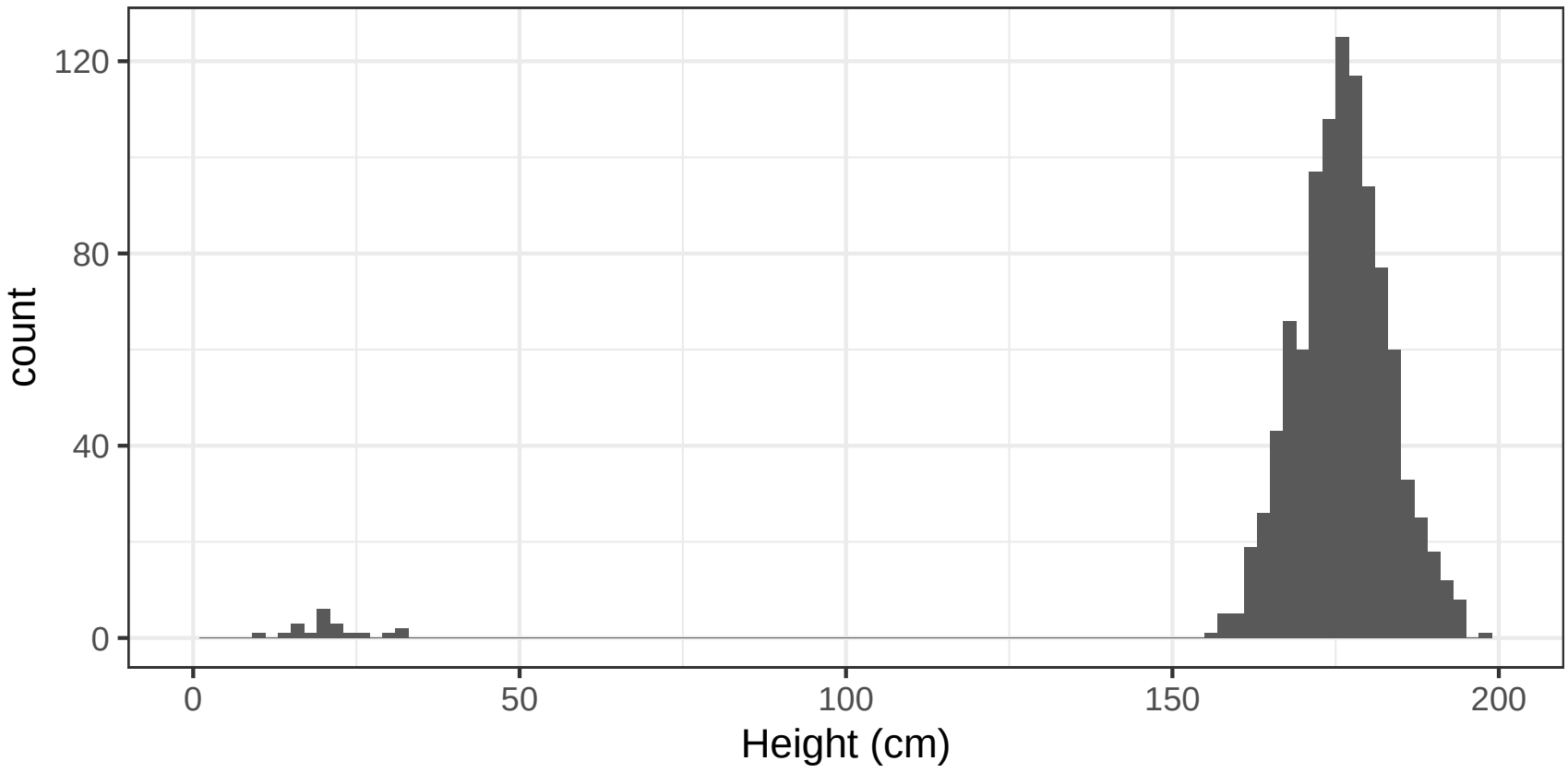
Potential QC issues:

- Biologically invalid values
- Extreme phenotypes
- Missing data
- Internal inconsistencies

And a lot of others you can't predict!

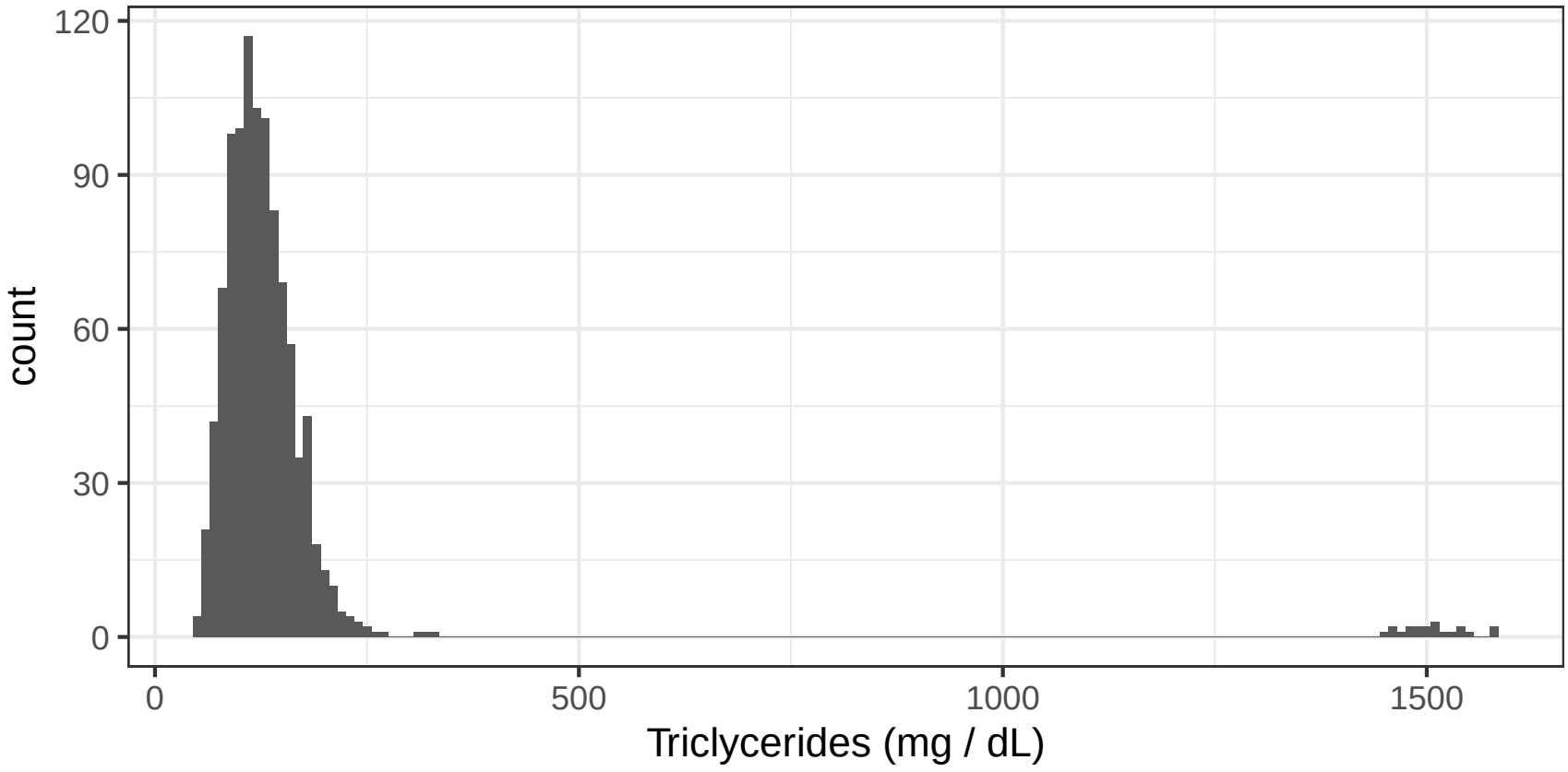
Are these values biologically invalid?

Example: Implausibly small height measurements



Are these extreme phenotypes true?

Example: Extreme triglycerides levels



Are any source phenotypes missing values?

Example: Missing data in some components for diabetes

	subject_id	diabetes_self_report	diabetes_meds
1	a	0	.
2	b	0	0
3	c	1	1
4	d	1	1
5	e	0	0
6	f	0	0
7	g	0	0
8	h	0	0
9	i	1	1
10	j	1	.

Are there any internal inconsistencies in the data?

Example: Self-reported vs. MD-diagnosed diabetes

	subject_id	self_report	md_diagnosis	
1	a	0	0	
2	b	1	1	
3	c	0	0	
4	d	0	0	
5	e	1	0	# discrepant
6	f	0	0	
7	g	1	1	
8	h	0	1	# discrepant
9	i	1	1	
10	j	1	1	

How do we fix problems?

- Which measurement (if any) is correct?
- Should you exclude subjects with discrepant data?
- Should outliers be excluded?
  - Measurement issue?
  - Real values indicative of rare variants with high effects (e.g., LOF)?

No blanket answer for all phenotypes!

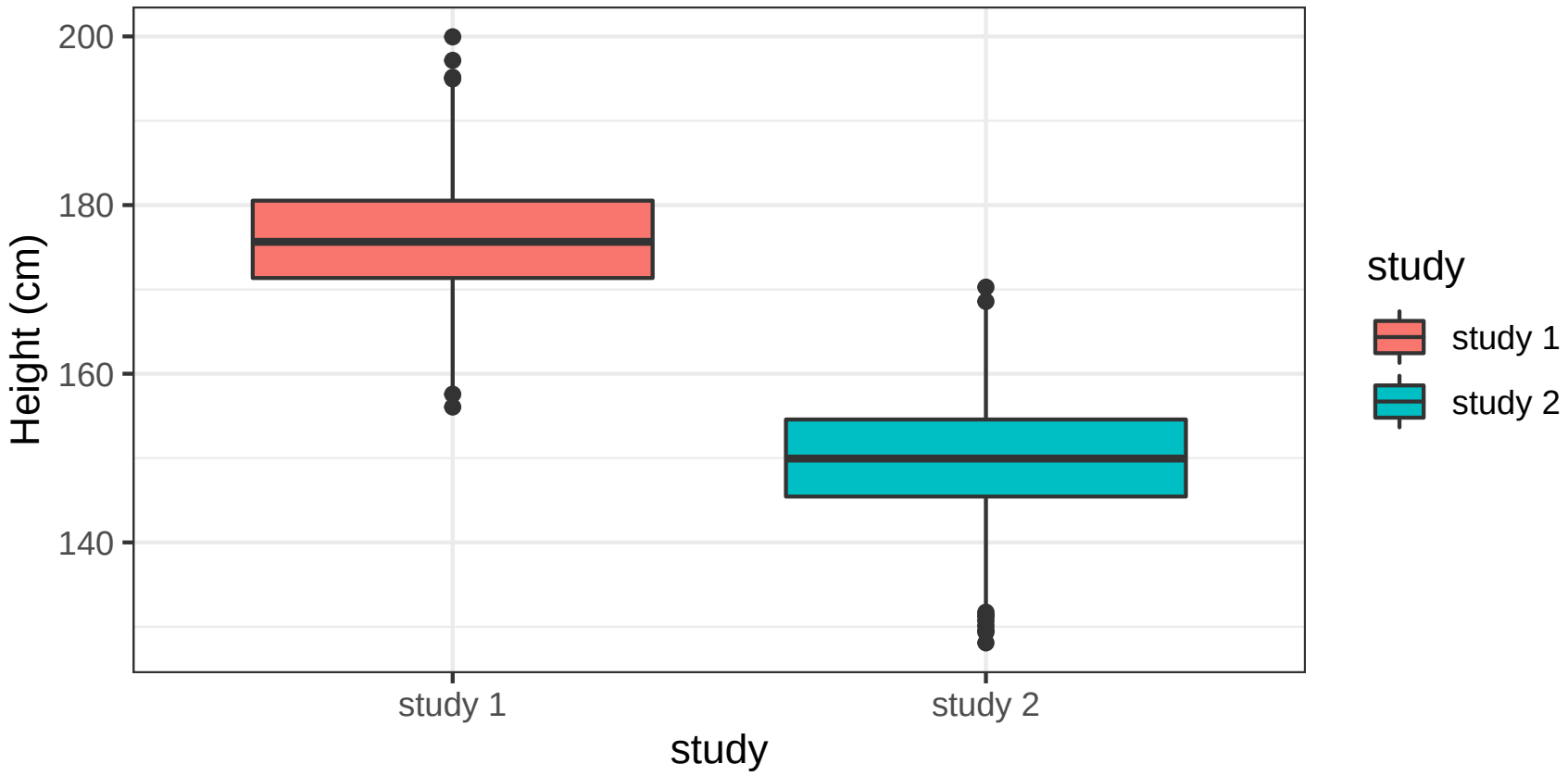
- Involve both study members and domain experts
- Clearly specify how you decide to handle these QC issues

QC of harmonized phenotypes

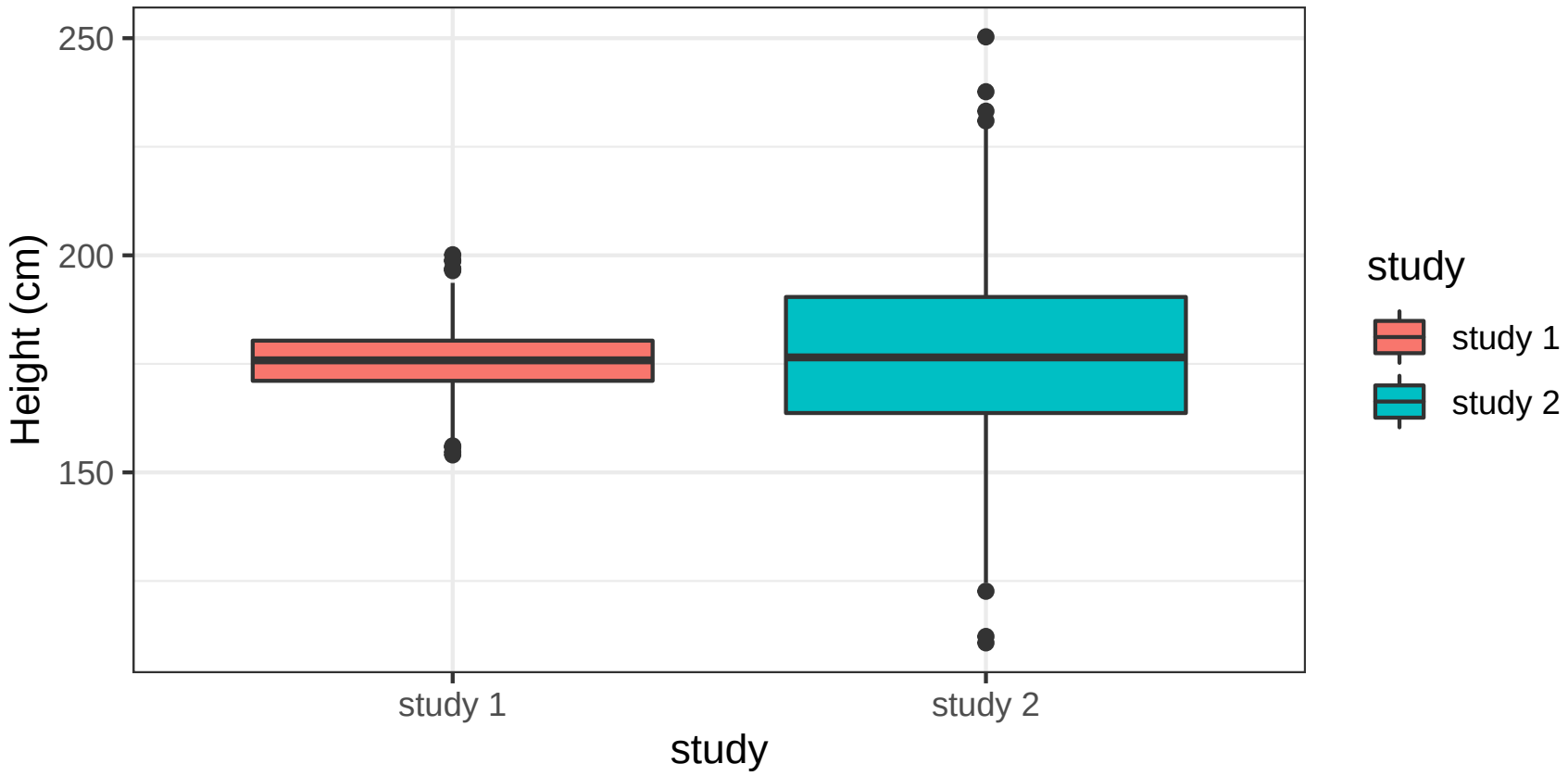
Are some studies very different than others?

- Quantitative phenotypes:
  - Mean
  - Standard deviation
  - General distribution
- Categorical phenotypes:
  - Frequency
- May need to look at batch effects from other variables, e.g.
  - Assay or device used?
  - Questionnaire version?
- Look at residual variance after fitting a null model
  - For WGS with related subjects, fit a mixed model
  - Fixed effects: age, sex, study
  - Random effects: genetic relatedness matrix

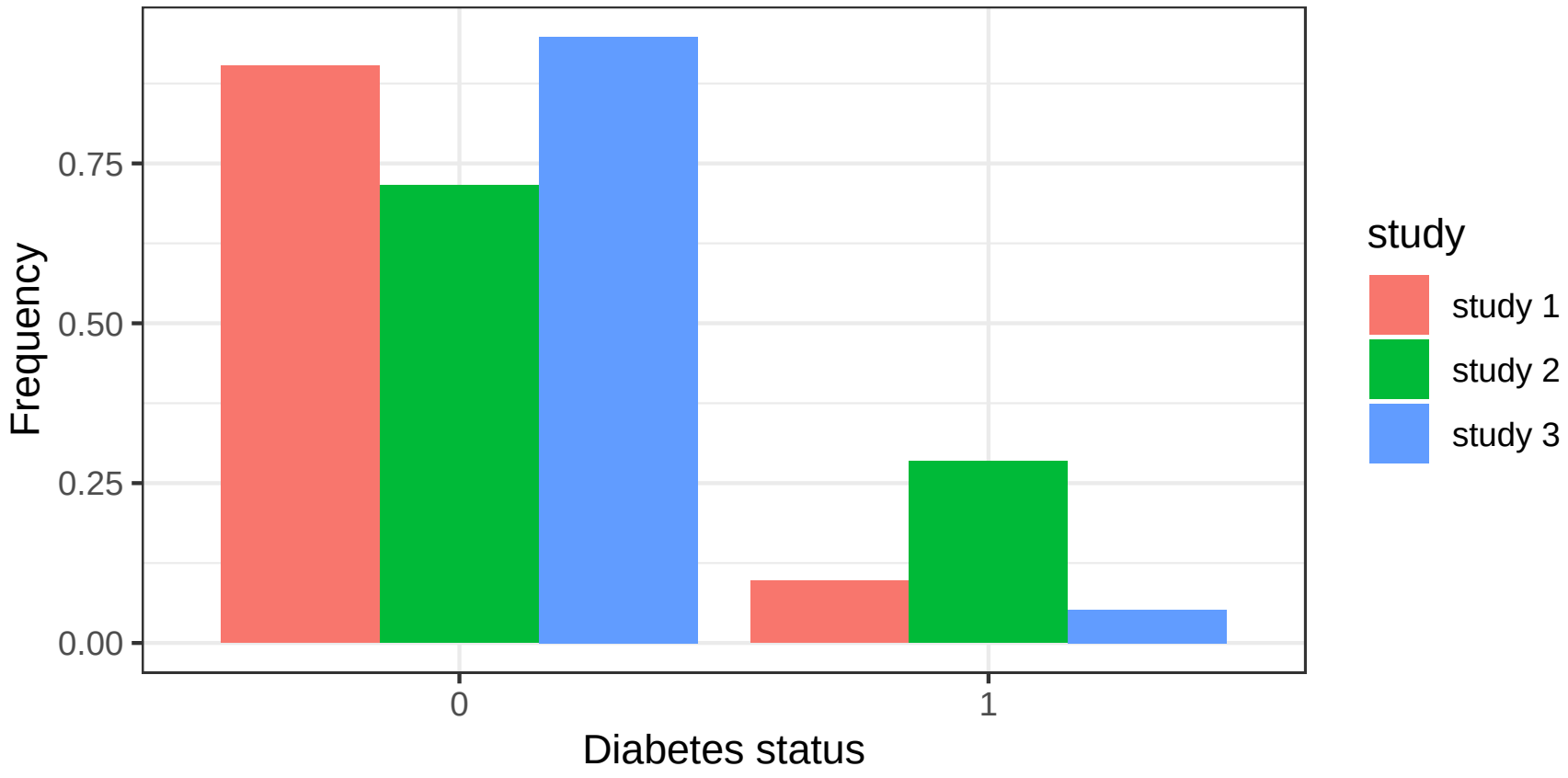
Do the studies have similar means?



Do the studies have similar standard deviations?



Do the studies have different frequencies?



What do you do if you find a difference between studies?

- Is there a valid reason for the difference?
  - Expected differences due to study design?
    - e.g. Higher prevalance of disease in a study targeting cases
  - Different distributions due to ancestry?
- Is there an error in the harmonization algorithm?
- Do you need to treat this study's data differently?
- Is the study too different to be included?
- Do you need to adjust for the difference in analysis?

Again, no blanket answer to these questions!

- Need to involve both study members and domain experts

Guidelines for Phenotype Harmonization

- Always use subject ids in phenotype files
  - Don't use sample ids (they may change if you detect a mixup)
- Decide who will do the harmonization
  - You or the studies?
- Provide clear instructions to the harmonizers
  - Description of target phenotype
  - Clear algorithm definition
  - How to handle missing data and QC issues
- Perform sanity checks on the files you receive
- Document, document, document!

Helpful references

- Bennett, SN et al. Phenotype harmonization and cross-study collaboration in GWAS consortia: the GENEVA experience. Genet Epidemiol. 2011 Apr; 35(3): 159-73
- Doiron, D et al. Data harmonization and federated analysis of population-based studies: the BioSHaRE project. Emerg Themes Epidemiol. 2013 Nov 21; 10(1): 12
- Fortier, I et al. Maelstrom Research guidelines for rigorous retrospective data harmonization. Int J Epidemiol. 2017 Feb 1; 46(1): 103-106