Observational Analysis in a *PetaByte* World

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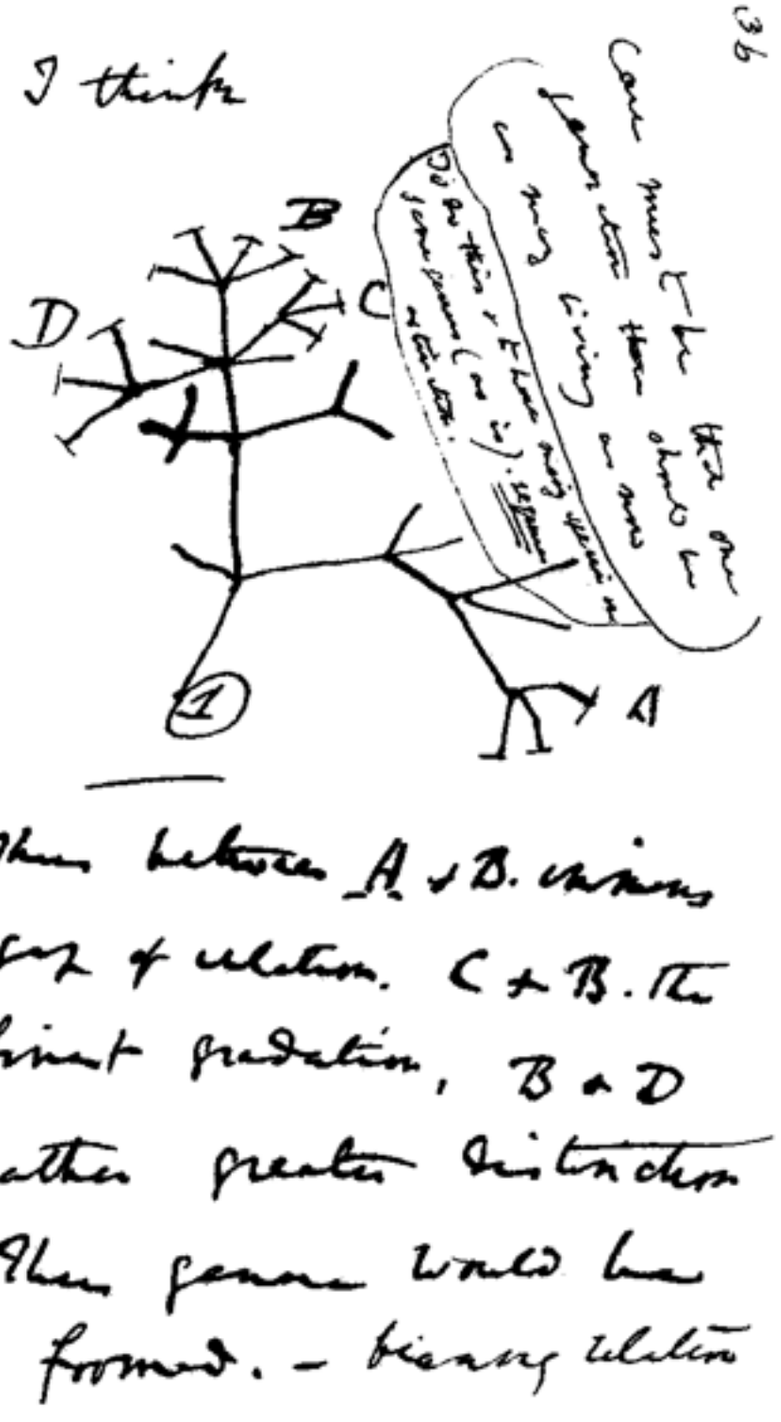
Discover. Educate. Care. Lead.

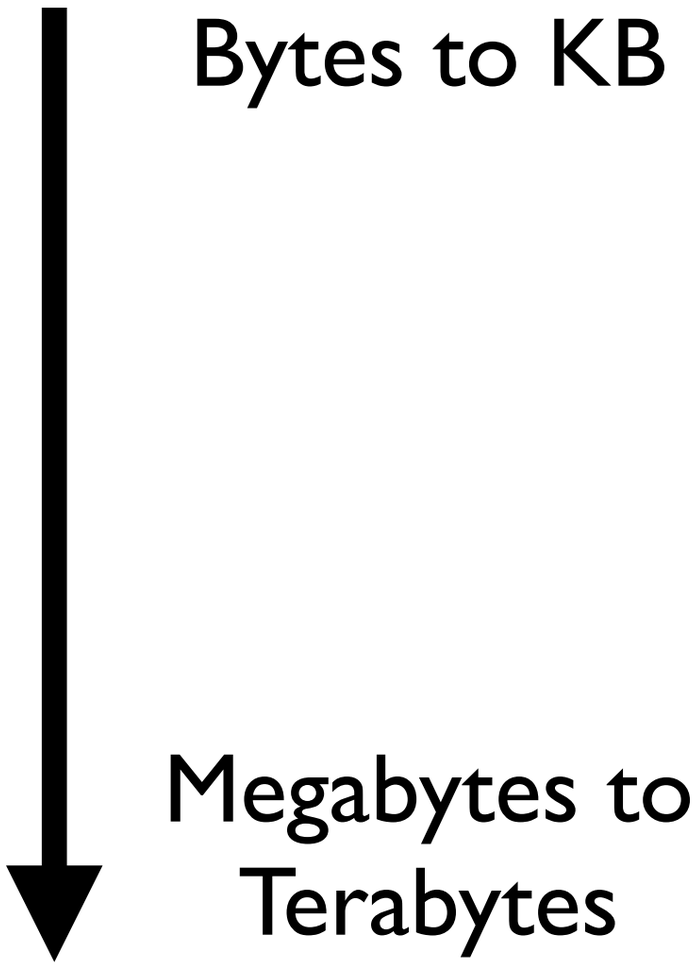
Observation is the starting point of biological discovery



- Charles Darwin observed relationship between geography and phenotype
- William McBride & Widukind Lenz observed association between thalidamide use and birth defects

The tools of observation are advancing

- Human senses
  - sight, touch, hearing, smell, taste
- Mechanical augmentation
  - binoculars, telescopes, microscopes, microphones
- Chemical and Biological augmentations
  - chemical screening, microarrays, high throughput sequencing technology



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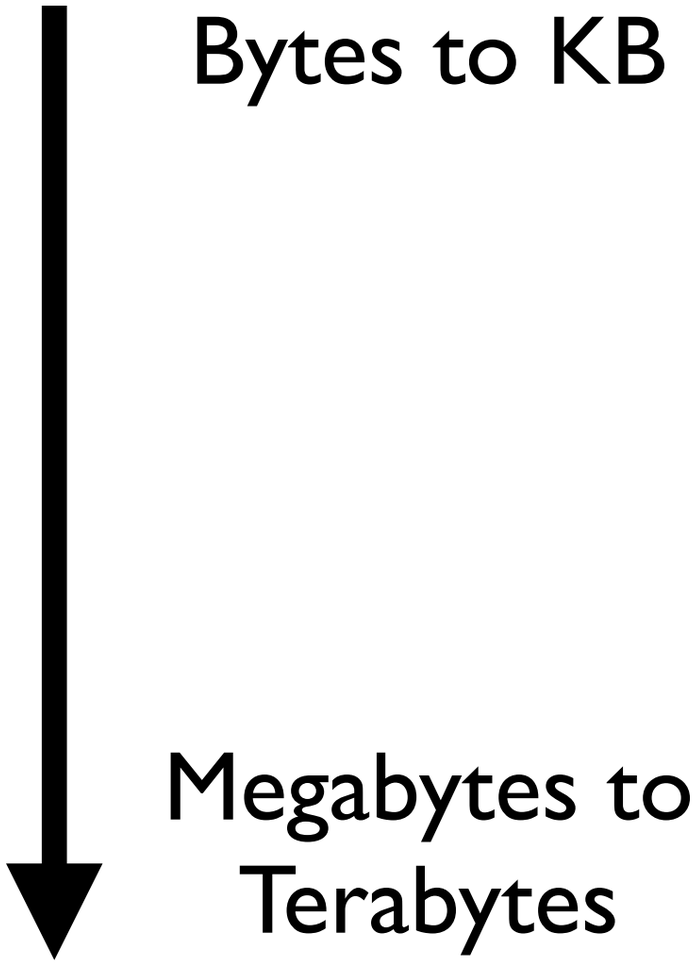
- What's next?



Technological Augmentation

- Tech companies are becoming *really good* at observing (and recording) the moments of life
  - Facebook
  - Google
  - Apple (iCloud)
  - **500 billion gigabytes** of information in the internet

Your doctor is observing you like never before

- Your local hospital is also observing and recording patient information
    - between 15 and 20% of primary care physicians are using electronic medical records
    - the average patient record has approximately 500,000 data points
    - that's over **300 thousand gigabytes** of health care data
- And there's more: Adverse Event Reporting System, National Health and Nutritional Examination Survey, etc.

Observation analysis in a *peta*byte world

- Darwin, McBride, and Lenz were working with *kilo*bytes of data
- Today's scientists are observing *tera*bytes and *peta*bytes of data
- The human mind simply cannot make sense of that much information
- Data mining is about making the tools of data analysis ("hypothesis generation") catch up to the tools of observation

Opportunity to study diseases and drugs *in vivo*

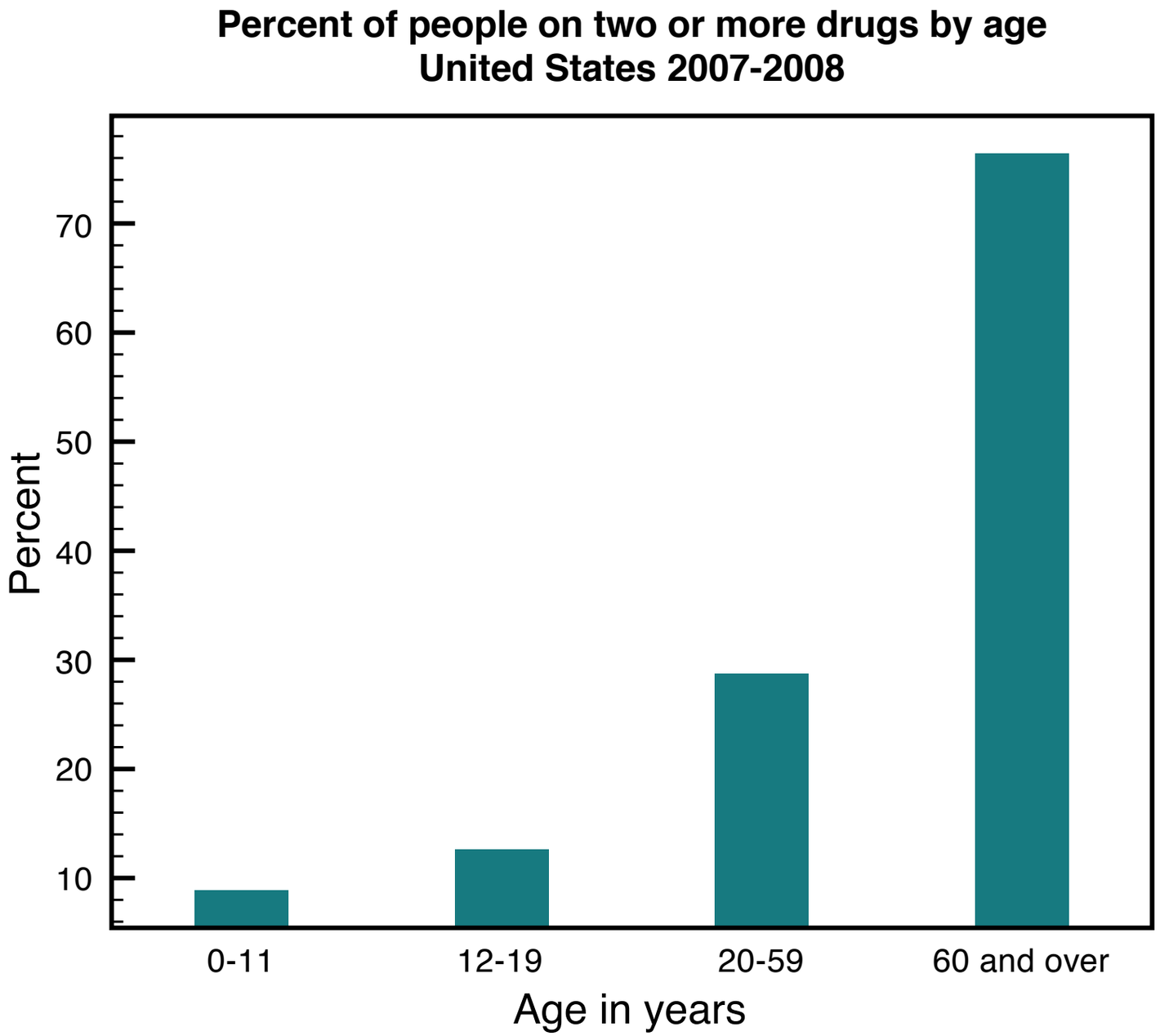
- enable the study of
    - drug-drug interactions
    - long term drug and disease effects
    - environmental exposures and health, etc.

Let’s focus on just one example...

Drug-drug interactions (DDIs)

- DDIs can occur when a patient takes 2 or more drugs
- DDIs cause unexpected side effects
  - 10-30% of adverse drug events are attributed to DDIs
- Understanding of DDIs may lead to better outcomes
  - precaution in prescription
  - synergistic therapies

Polypharmacy increases with age



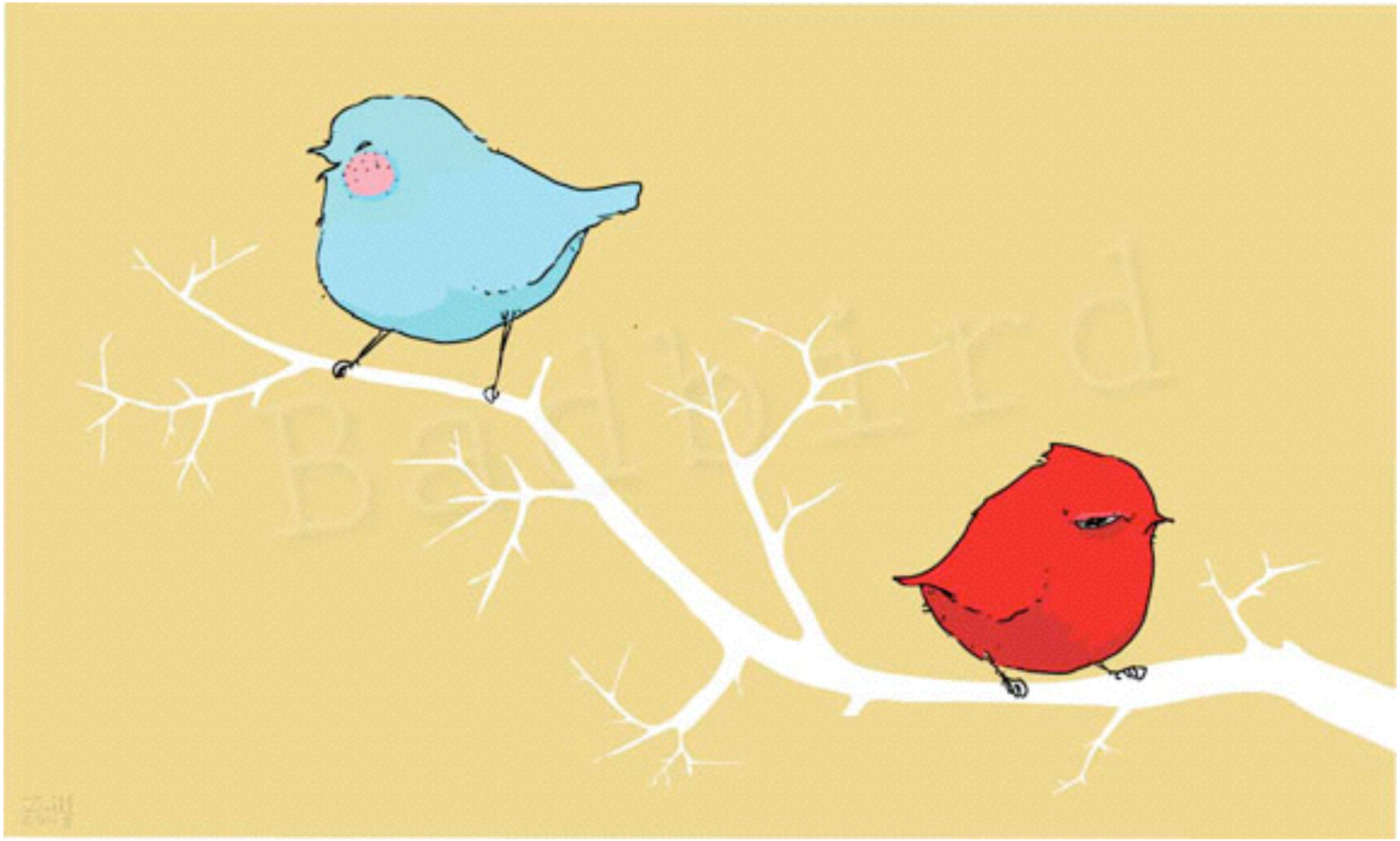
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey

76% of older Americans used two or more prescription drugs

More needs to be done to understand and identify drug-drug interactions

- Clinical trials do not typically investigate drug-drug interactions
- **Observational studies** are the only systematic way to detect drug-drug interactions

Bias confounds observations



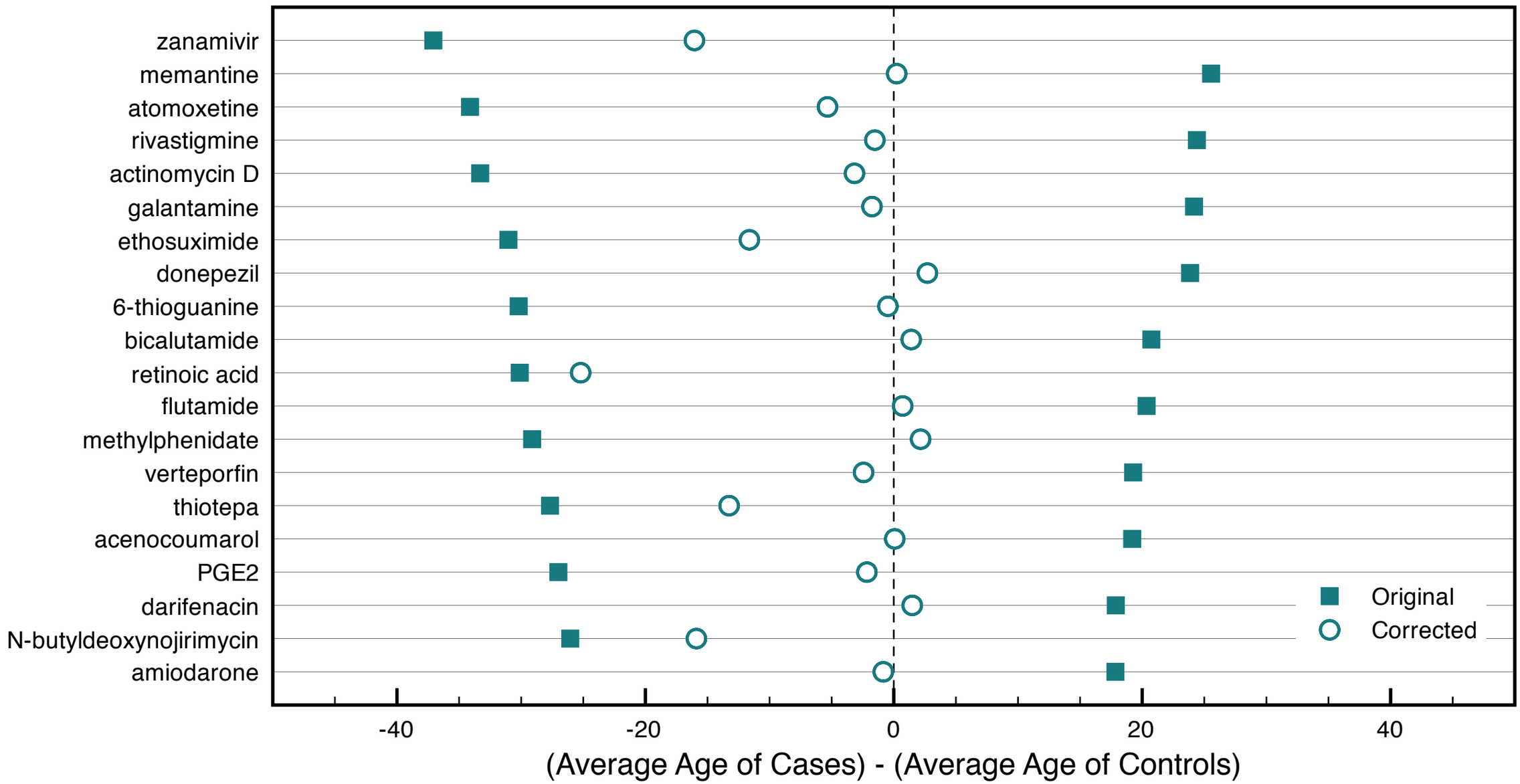
Bias confounds observations

- Males have more “penile swelling” than females
  - Drugs given primarily to **males** are more likely to be observed with **penile swelling**

Statistical Correction of Uncharacterized Bias

- A new statistical model for correcting bias in large observational data sets
    - leverages size of data and internal covariances to correct bias
- (!) do not need to know where the bias is coming from

Method corrects for unmeasured age effects

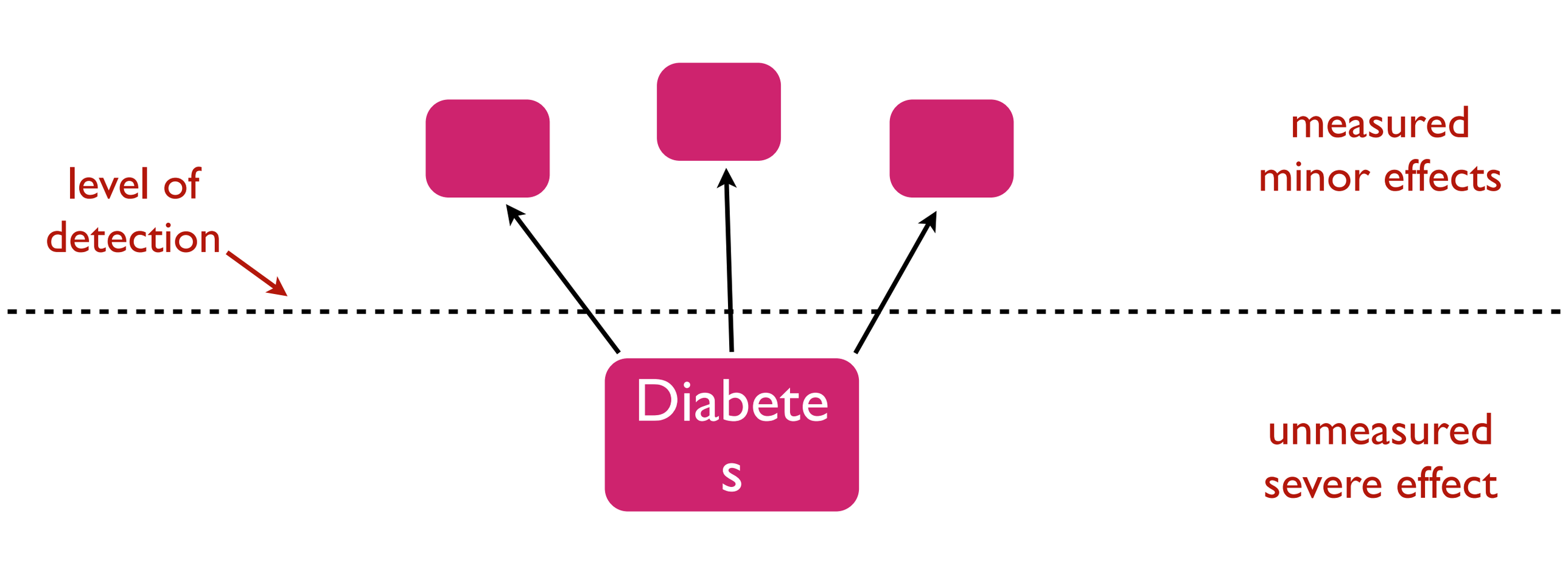


Missing data limits utility of observational data

- Nothing can be done with diseases and drug effects that are never observed or recorded

Latent Signal Detection

- The human system is a complex and interwoven network of pathways and systems



Latent model of Diabetes Risk

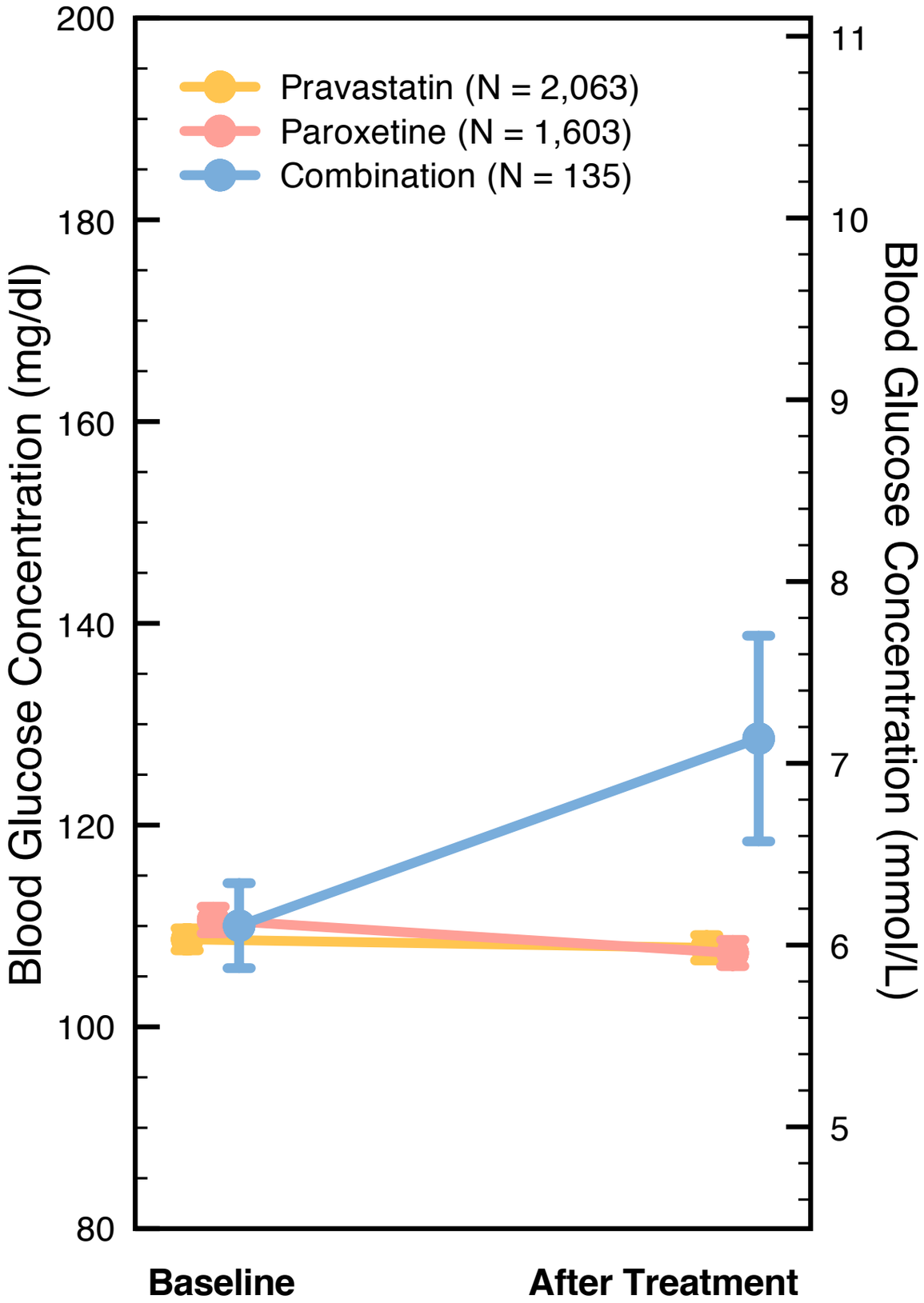
- Identified putative interaction between paroxetine and pravastatin
- Using the Electric Medical Records
  - *Validation* of putative drug interactions

Analyzed blood glucose values for patients on either or both of these drugs

Stanford

Vanderbilt

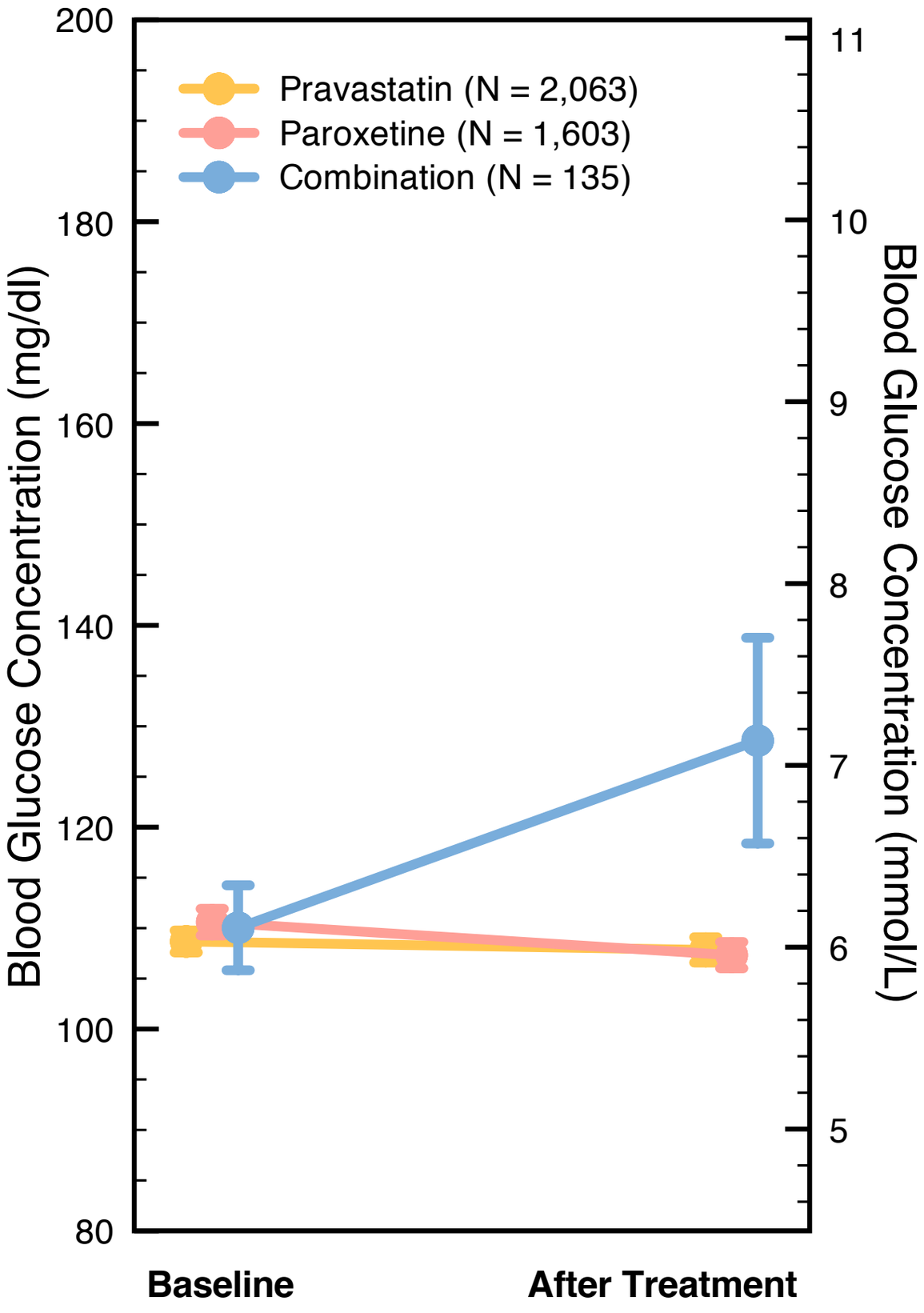
Harvard



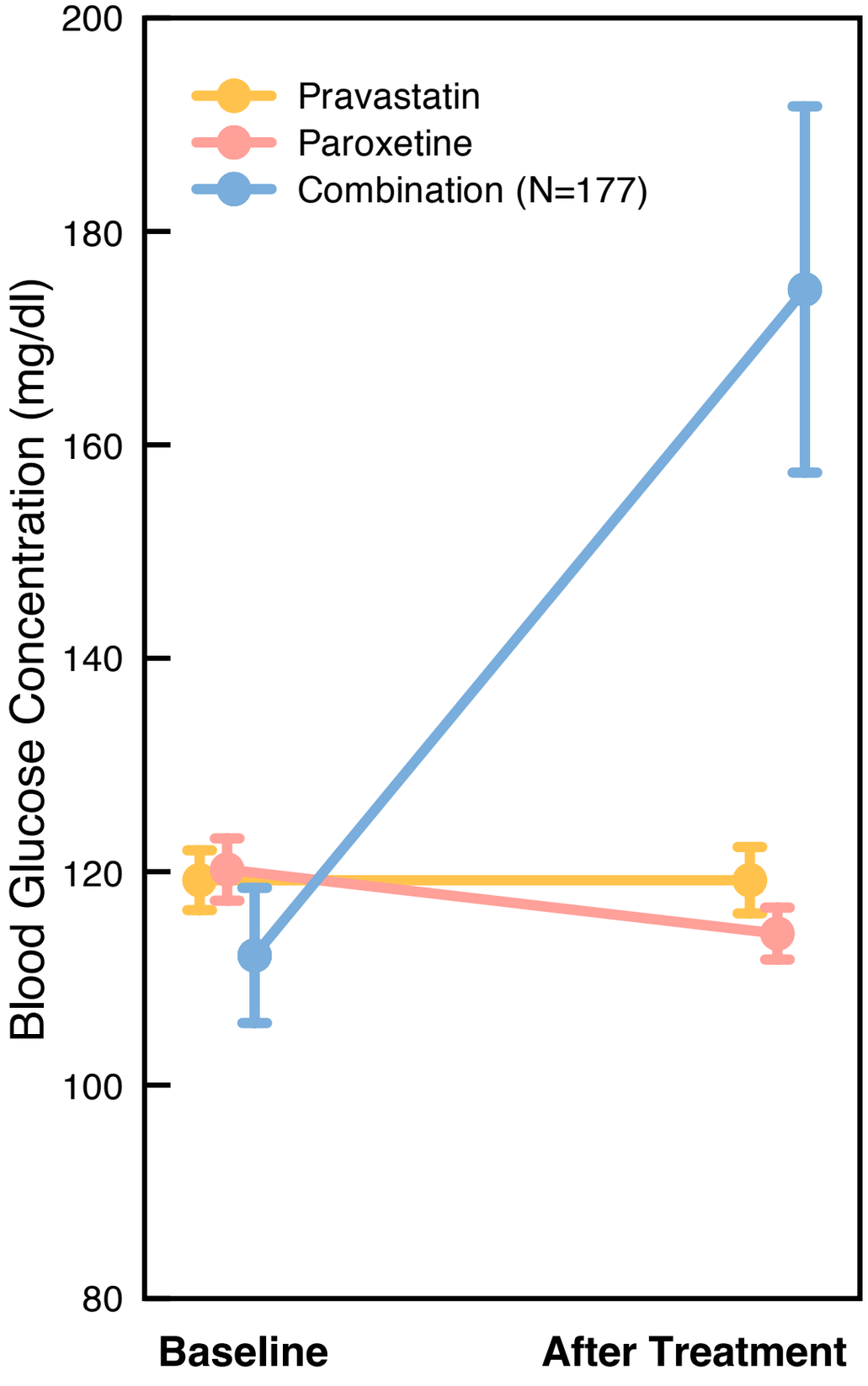
+18 mg/dl incr.
$p < 0.001$

Tatonetti, et al. 2011 Clinical Pharmacology & Therapeutics

no diabetics



including diabetics



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Data mining is hypothesis generation...

- associations found by DM are **not** biological truth
- DM methods should be evaluated by their ability to produce concrete testable hypothesis
- the simpler and more straightforward the hypotheses are to test the better the method

Observational analysis in a *petabyte* world

- Enormous data provide enormous opportunity
- But only through careful consideration of the biases can insight be gleamed
  - The age of theory is not dead

Observational analysis leads to biological discovery

- Correction for unknown or uncharacterized bias in observational data
- Discovery of latent adverse events through their associated side effects
- We can use the EMR to corroborate putative DDIs
- The advent of Garage Data Science is upon us!

Thank you

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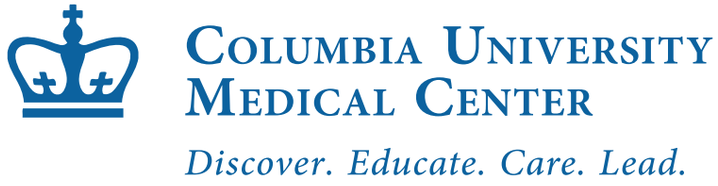
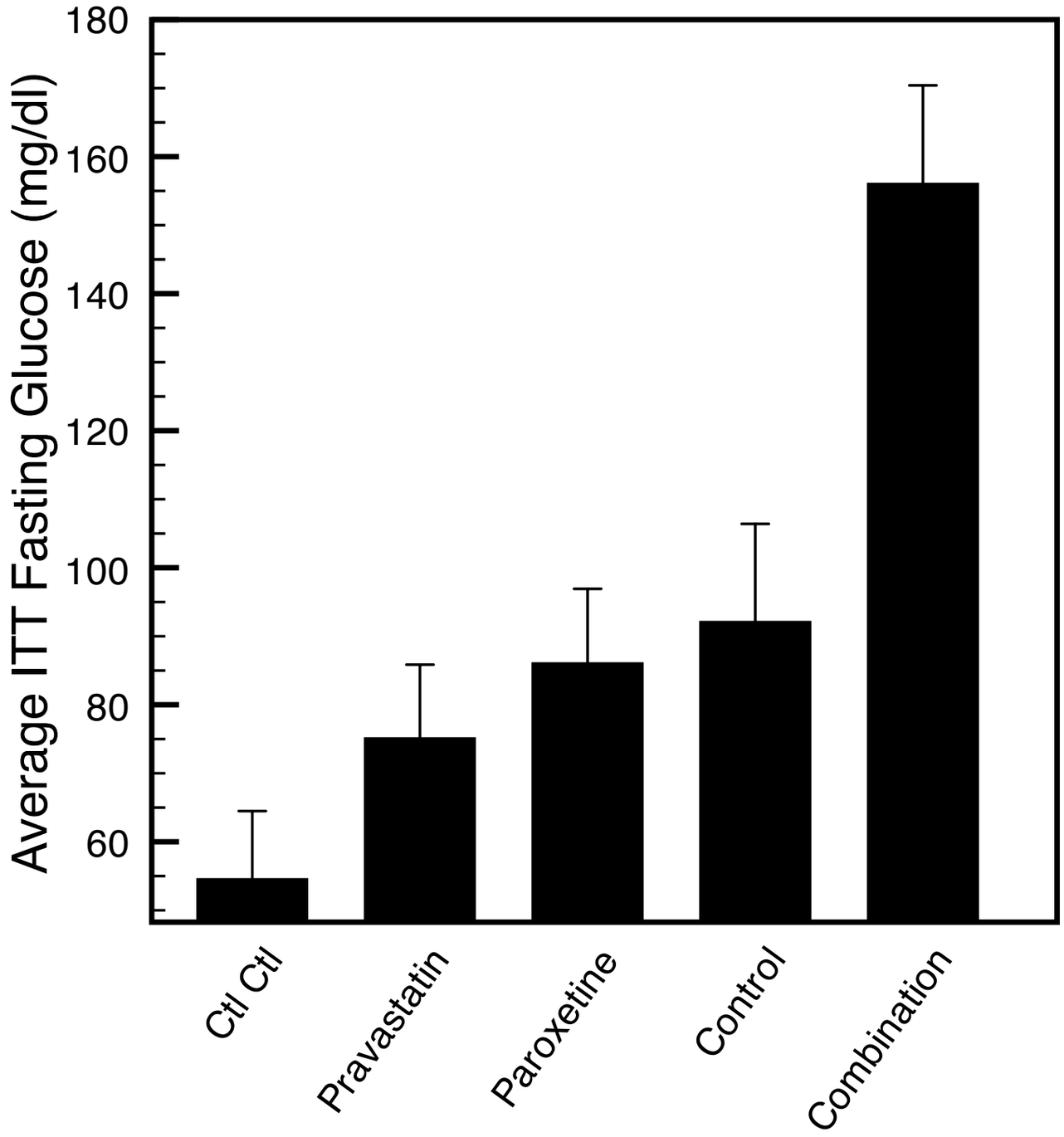


Informatics methods have taken us far, skeptics remain

- Insulin Resistant Mouse Model
  - 10 control mice on normal diet (Ctl Ctl)
  - 10 control mice on high fat diet (HFD)
  - 10 mice on pravastatin + HFD
  - 10 mice on paroxetine + HFD
  - 10 mice on combination + HFD

Simulating Pre-Diabetics

Summary of fasting glucose levels



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