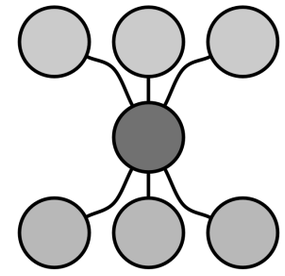

Data analytics approaches to enable ***EWAS***

Chirag J Patel and Nam Pho

Emory Exposome Workshop

06/16/16

HARVARD MEDICAL SCHOOL

DEPARTMENT OF Biomedical Informatics

chirag@hms.harvard.edu

@chiragjp

www.chiragjpgroup.org

Extensible & open-source analytics software library
(*XWAS R package*)

Freely available *exposome* data for your research
(NHANES: 40,000 individuals and 1,000 variables)

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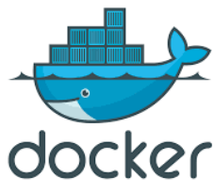
XWAS **+**  **+**  **=** ***goodness!***

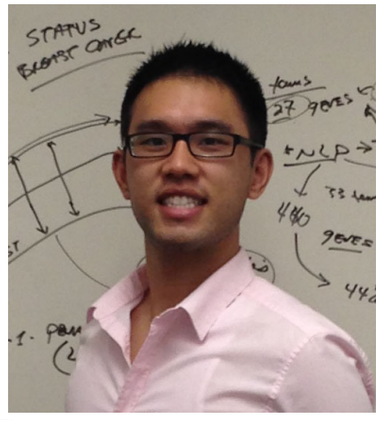
http://bit.ly/exposome-analytics-course

Please let us know if you are using the resources
(or provide feedback)!

Chirag

@chiragjp

Nam



@nampho2

Real quick:

What is the *exposome*? What is the *phenome*?

exposome

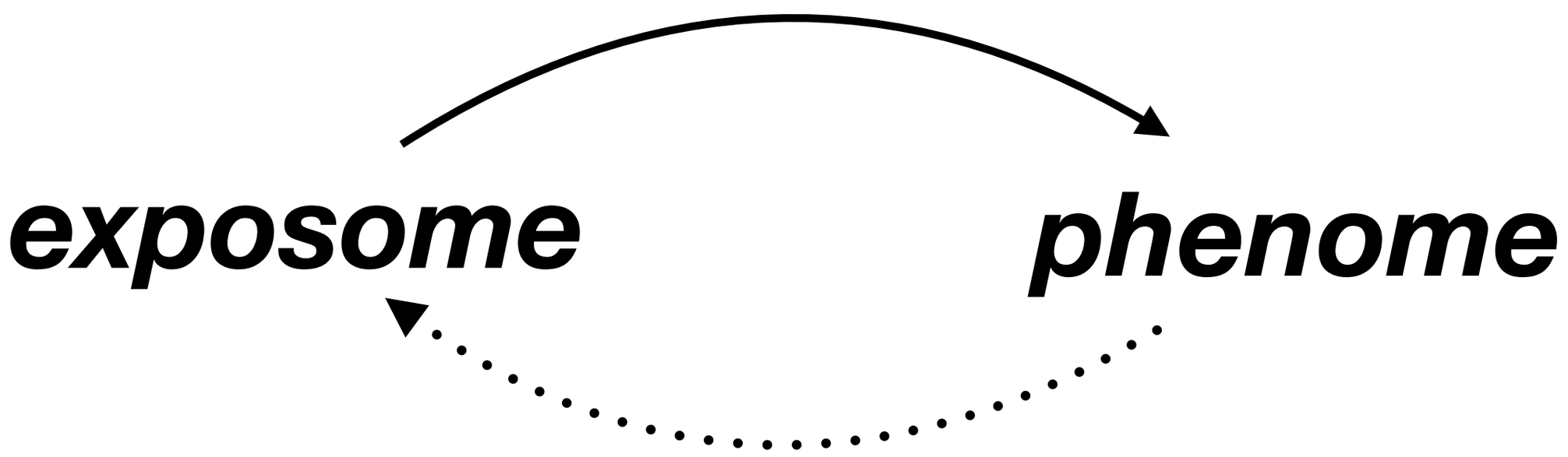
internal	external
lead (serum)	geography
nutrients (serum)	air pollution
infection (urine)	income
metabolome	

phenome

function	diseases
expression	diabetes
telomeres	cancer
metabolome	heart disease

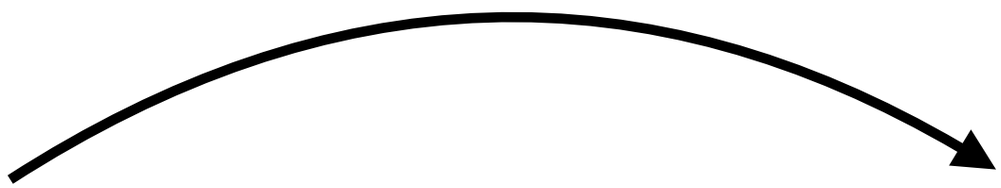
Exposome associated with the ***phenome***?

…and vice versa?



Analytic **tools** and big data **infrastructure** required to associate *exposome* with *phenome!*

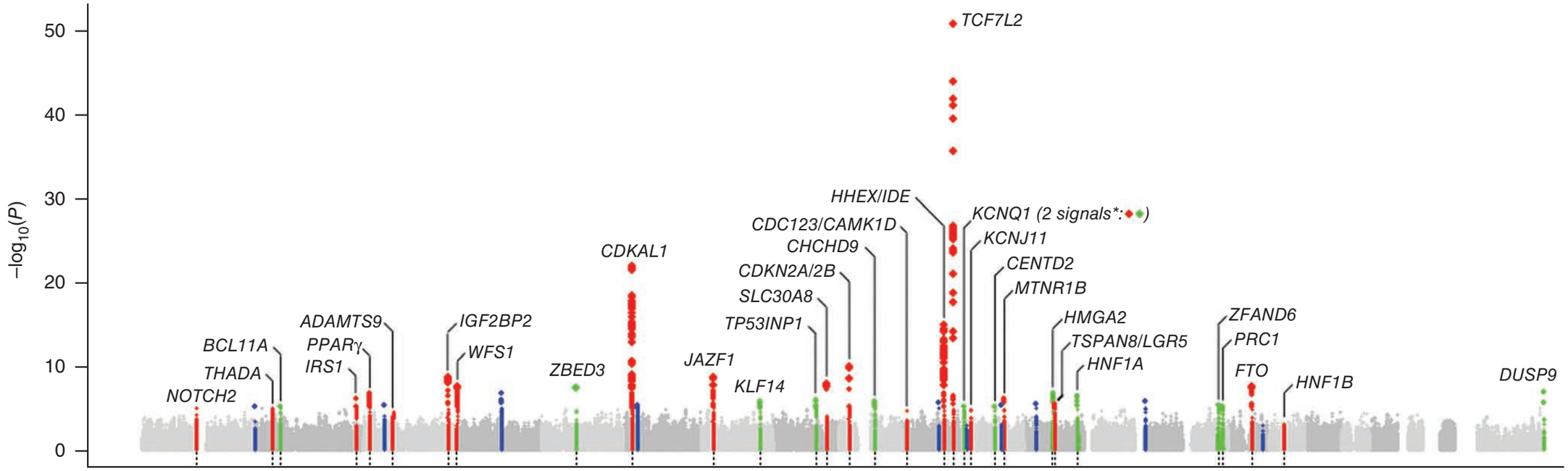
We can learn a thing or two from ***genomics*** investigation…



genome ***phenome***

e.g., ***GWAS***

Big data approaches fueled discovery of genetic variants in disease (example: genome-wide association [**GWAS**])



GWAS in Type 2 Diabetes

Voight et al, Nature Genetics 2012

N=8K T2D, 39K Controls

A search engine for robust, reproducible genotype-phenotype associations…

There are ***non-trivial*** data analytic challenges in searching for exposome-phenome associations!

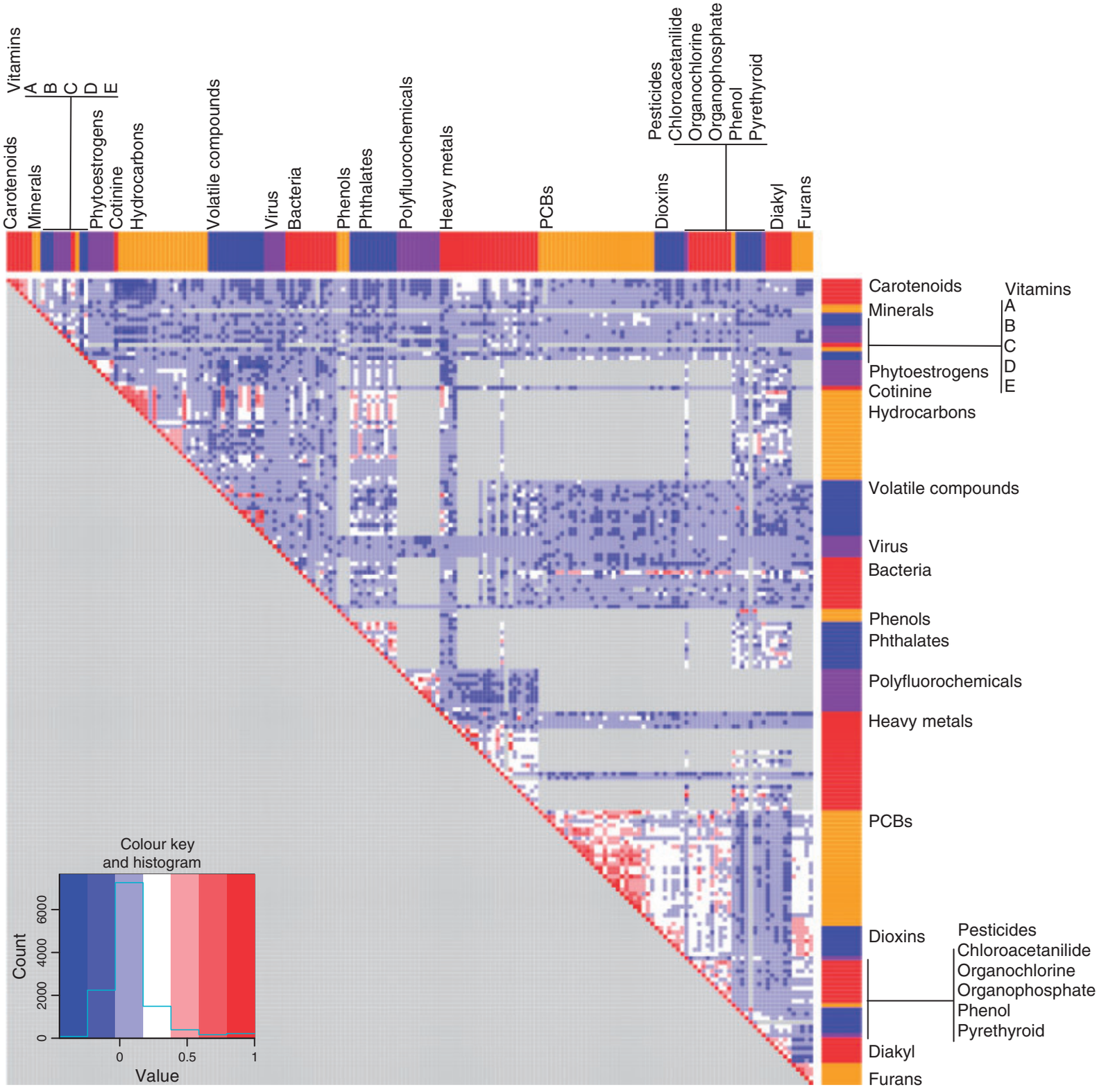
JAMA 2014
Pac Symp Biocomp 2015

Dense correlational web!

what causes what?

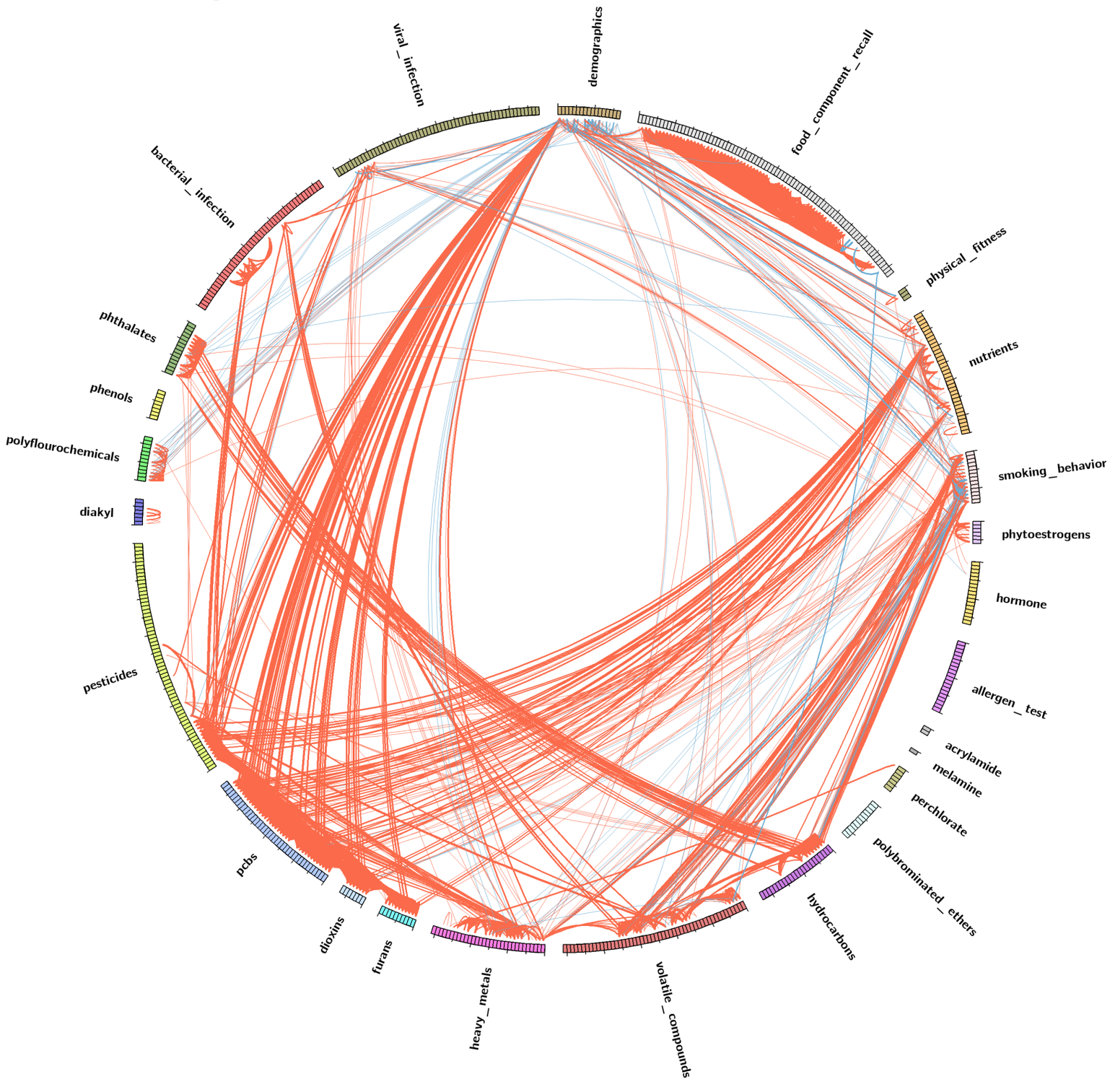
confounding bias?

JAMA 2014
Pac Symp Biocomp 2015


Vitamins
A
B
C
D
E
Carotenoids
Minerals
Phytoestrogens
Cotinine
Hydrocarbons
Volatile compounds
Virus
Bacteria
Phenols
Phthalates
Polyfluorochemicals
Heavy metals
PCBs
Dioxins
Pesticides
Chloroacetanilide
Organochlorine
Organophosphate
Phenol
Pyrethyroid
Diakyl
Furans
Colour key
and histogram
Count
0
2000
4000
6000
0
0.5
1
Value

IJE 2013

Interdependencies of the ***exposome***: Correlation globes paint a complex view of exposure



http://bit.ly/globebrowse

Pac Symp Biocomput. 2015
JECH. 2015

Multiplicity: how to determine signal from noise?

type 1 error (spurious findings)

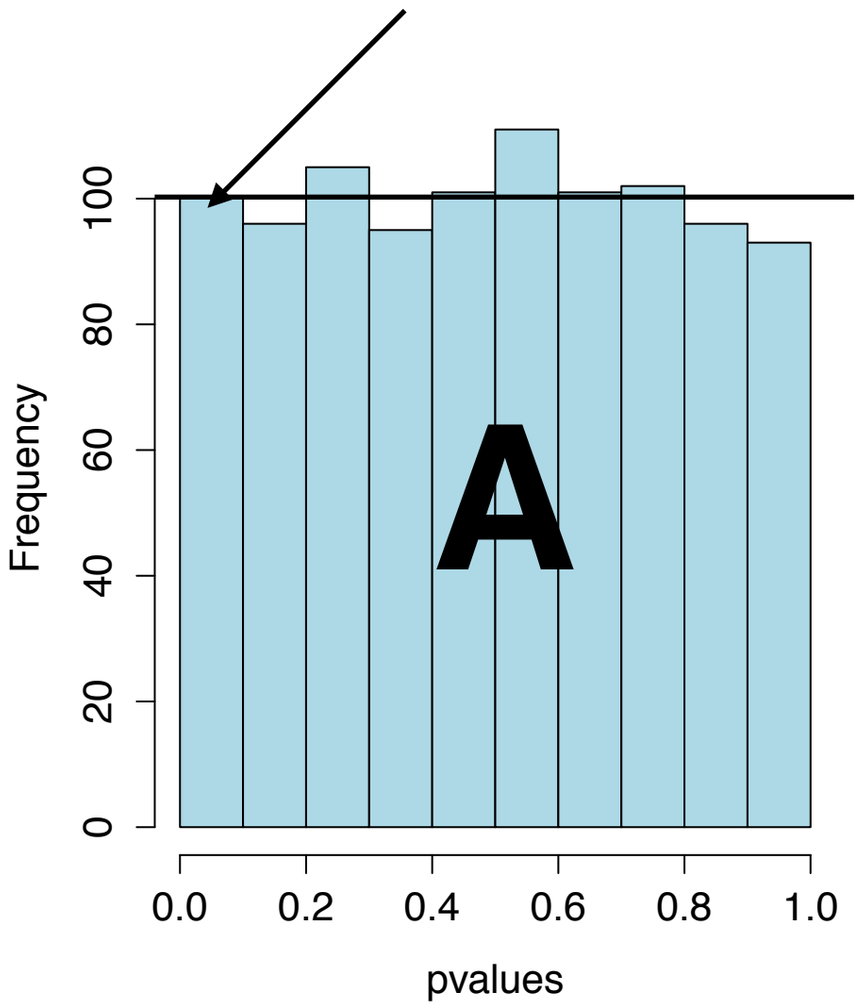
JAMA 2014

Suppose you are testing 1000 exposures in case-control study (disease vs. healthy)…

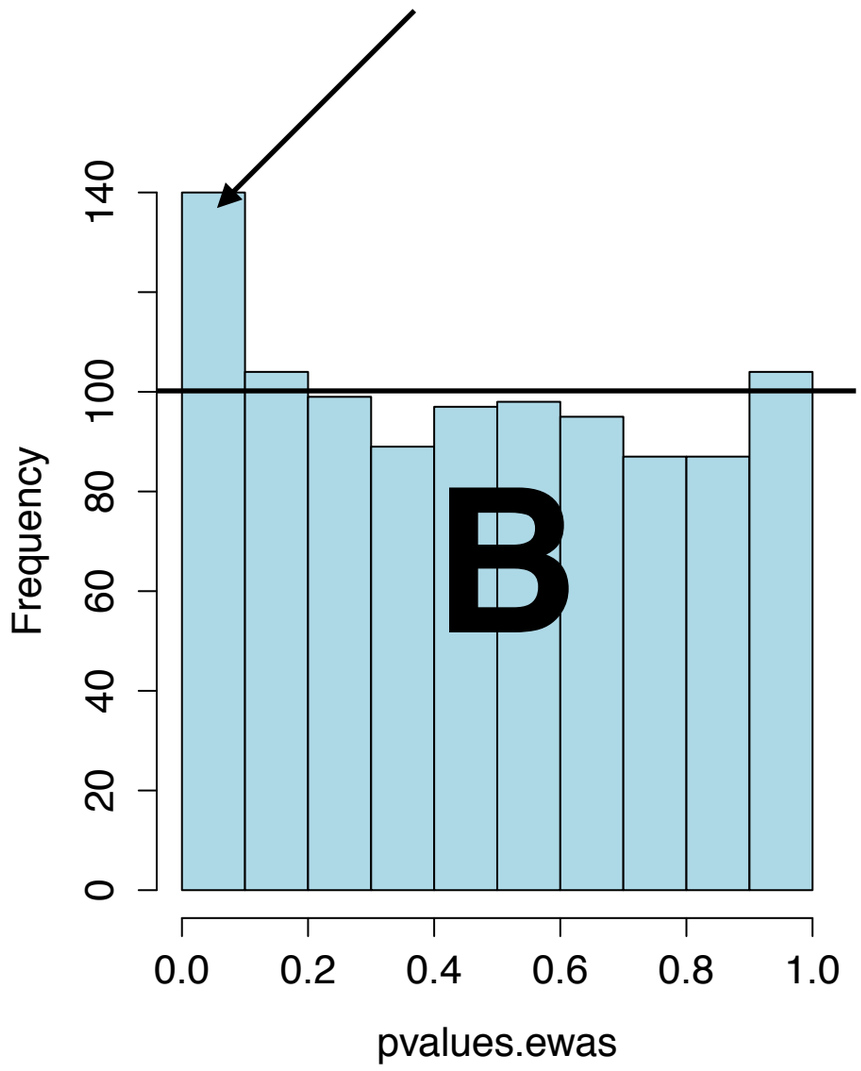
… and there were no difference between the cases and controls…

…how many findings would be “significant” at a p-value threshold of 0.05 (due to chance)?

Regime of multiple tests and "*signal to noise*":
Histogram of p-values in 2 scenarios: no difference and 5% different



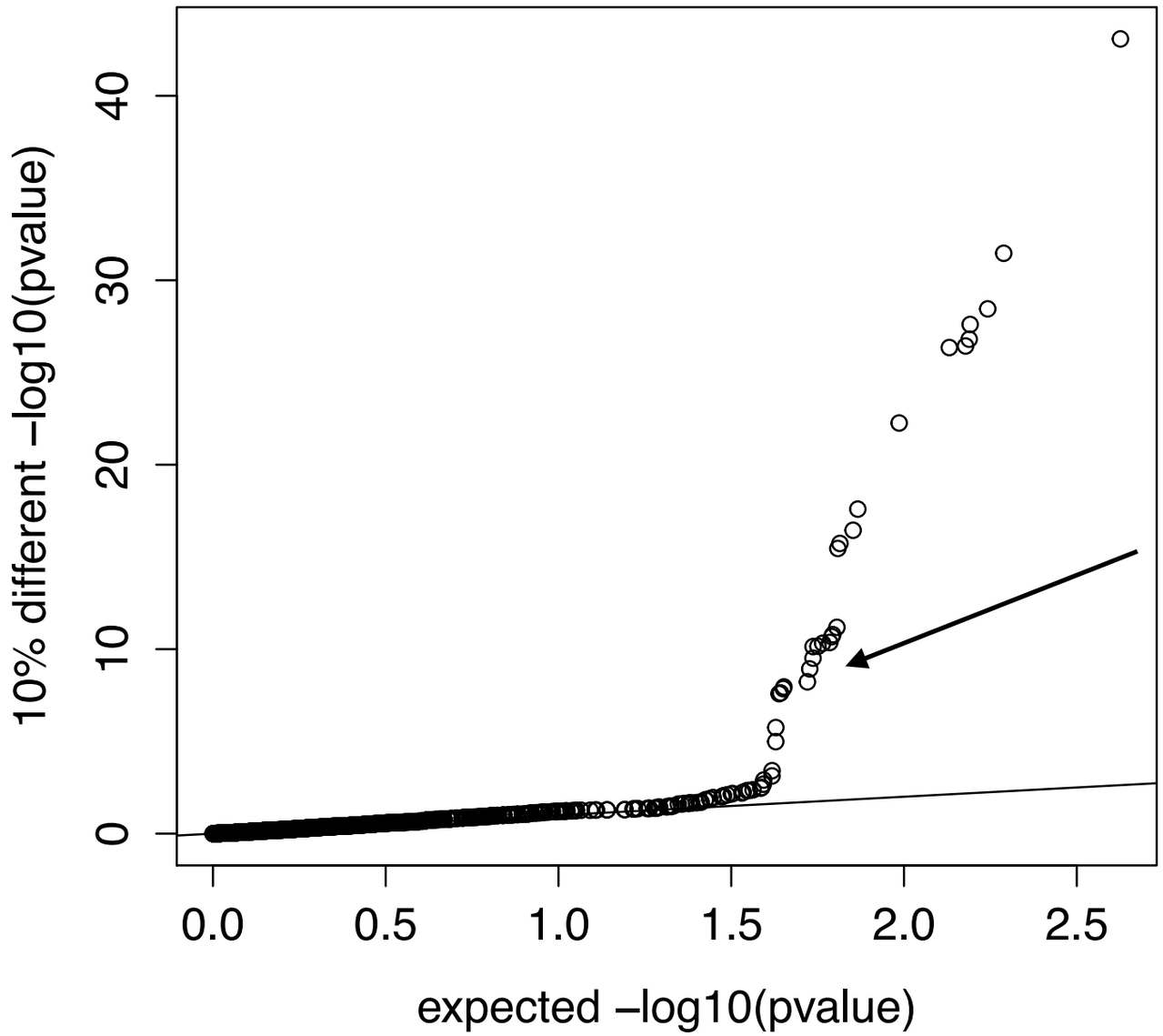
No difference
(no true associations)



5% exposures different
(5% true associations)

Estimating the deviation from null:
QQplot: -log10(pvalues) in the null and *EWAS* distributions

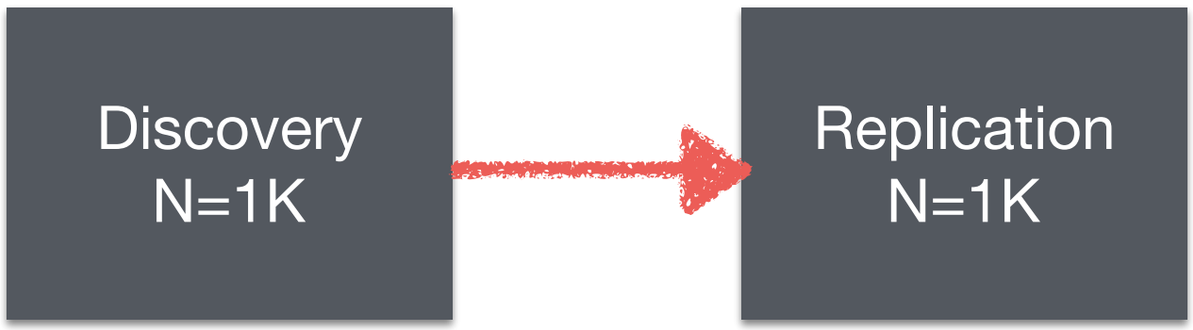
B



A

Bonferroni
False discovery rate

The tension between type 1 and type 2 errors: ***Power*** and ***replication*** for robust associations!

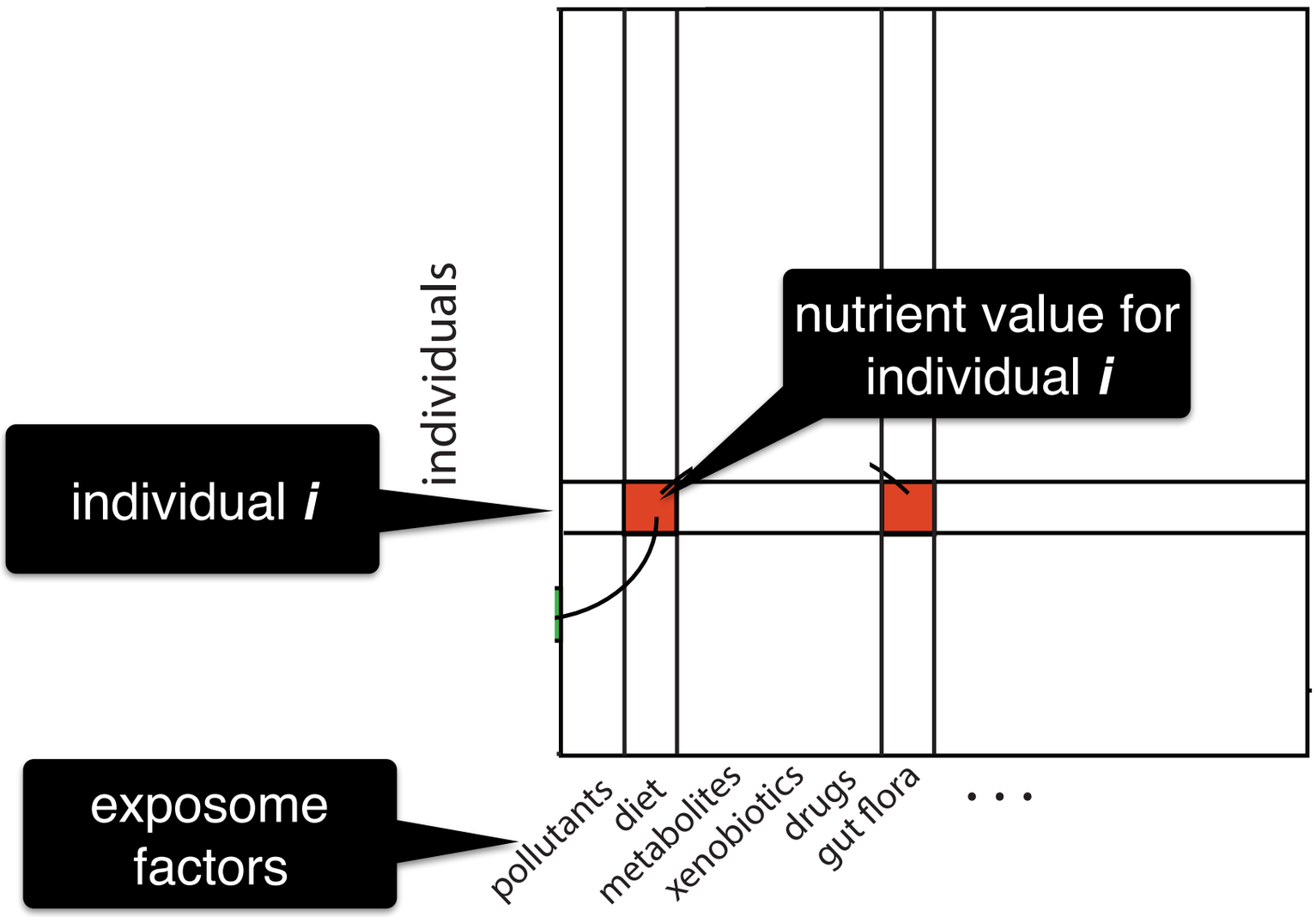


Discovery sample sizes must be large to overcome ***multiple testing*** and mitigate ***winner's curse***

Replication sample size must be large to detect association

What will the ***exposome*** data structure look like?:

a ***high-dimensioned 3D*** matrix of
(1) ***exposure*** measurements
on (2) ***individuals*** as a function of (3) ***time***



in review

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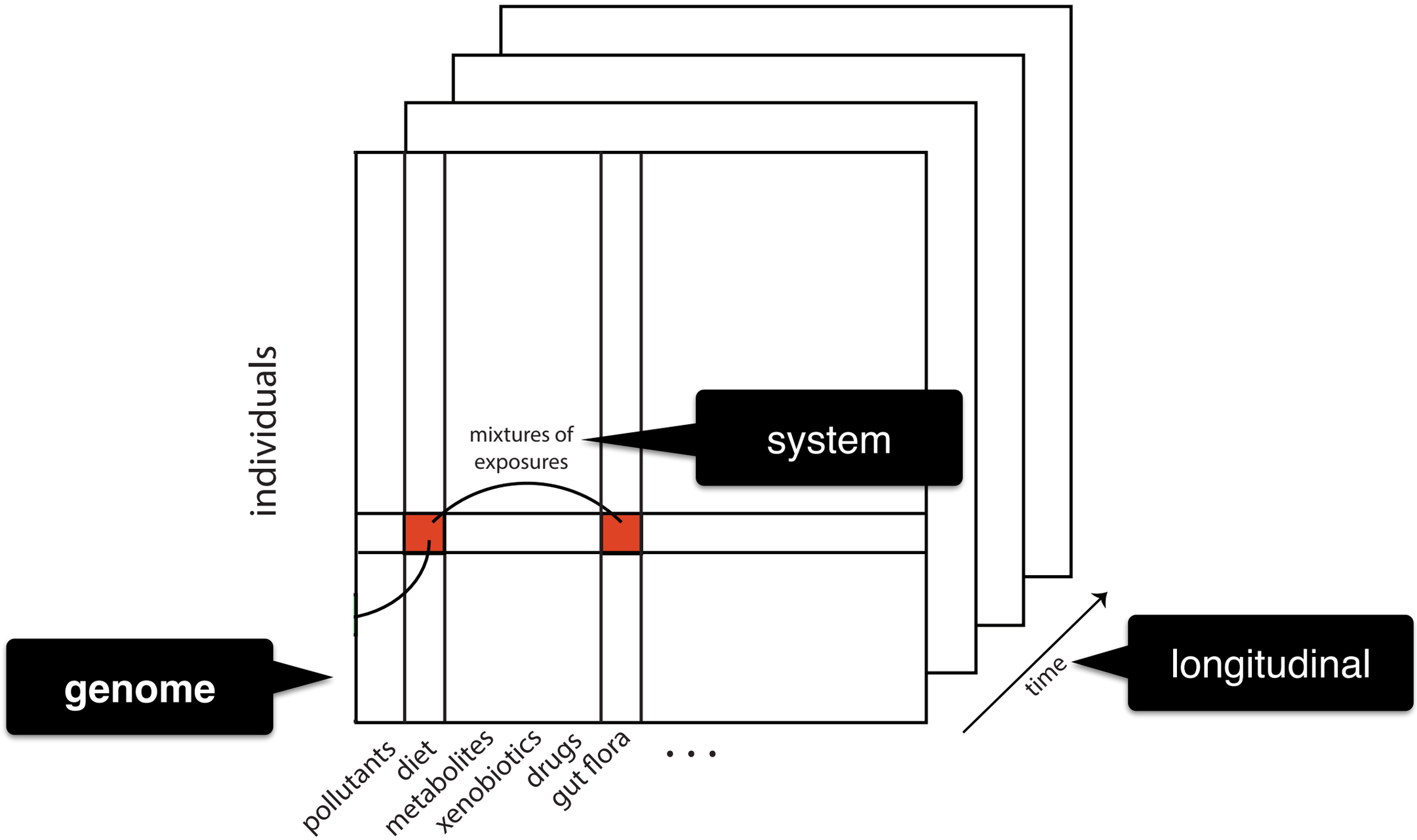
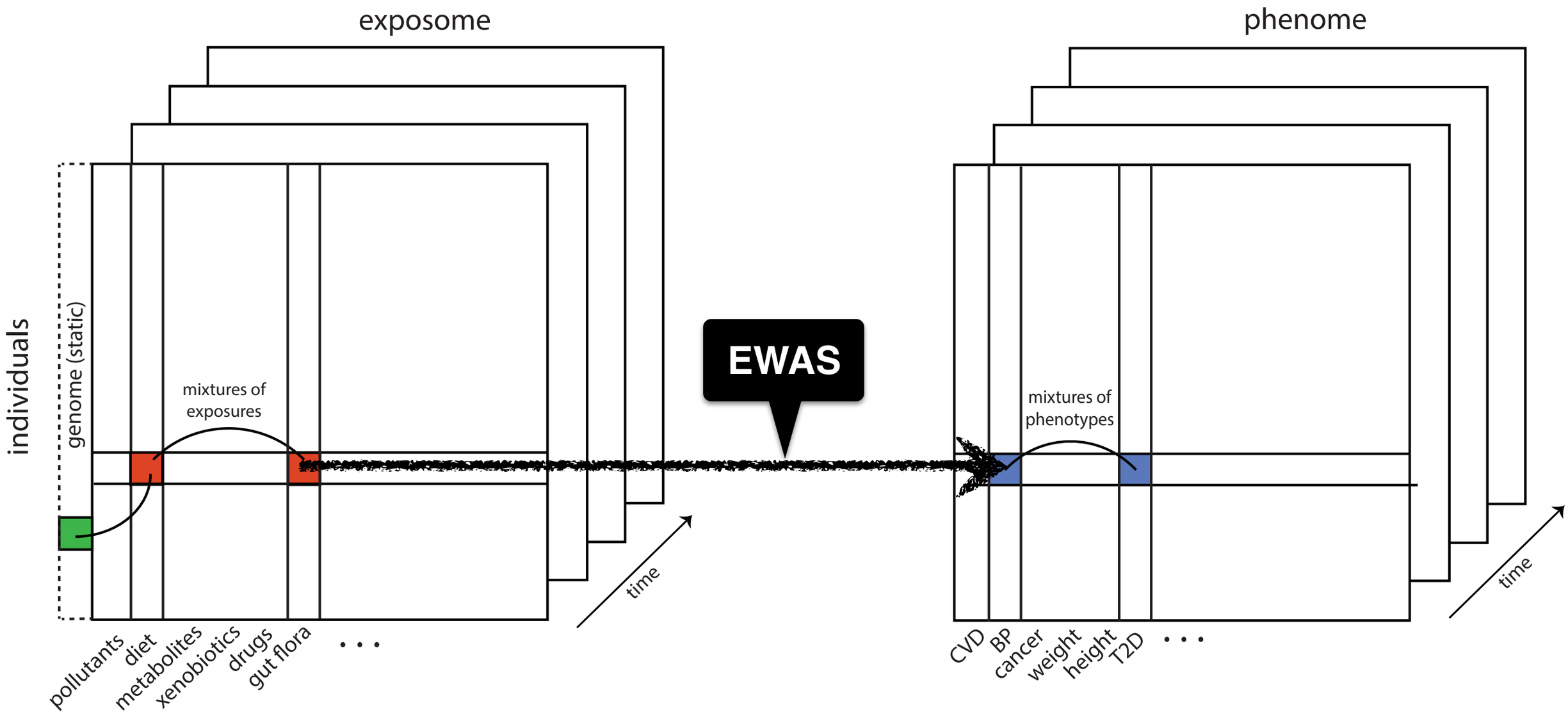


in review

A schematic of a data-driven search for ***exposome-phenome*** associations…



in review

Time for you to give it a try!

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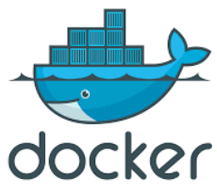
XWAS **+**  **+**  **=** ***goodness!***

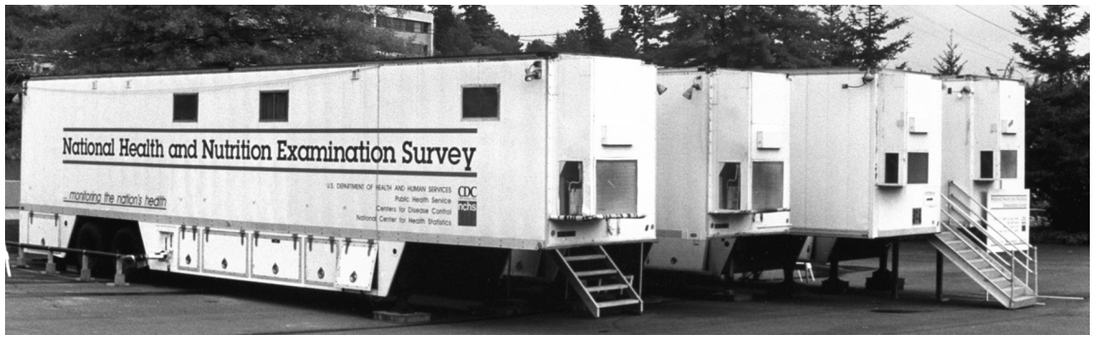
Fully merged dataset:
National Health and Nutrition Examination Survey

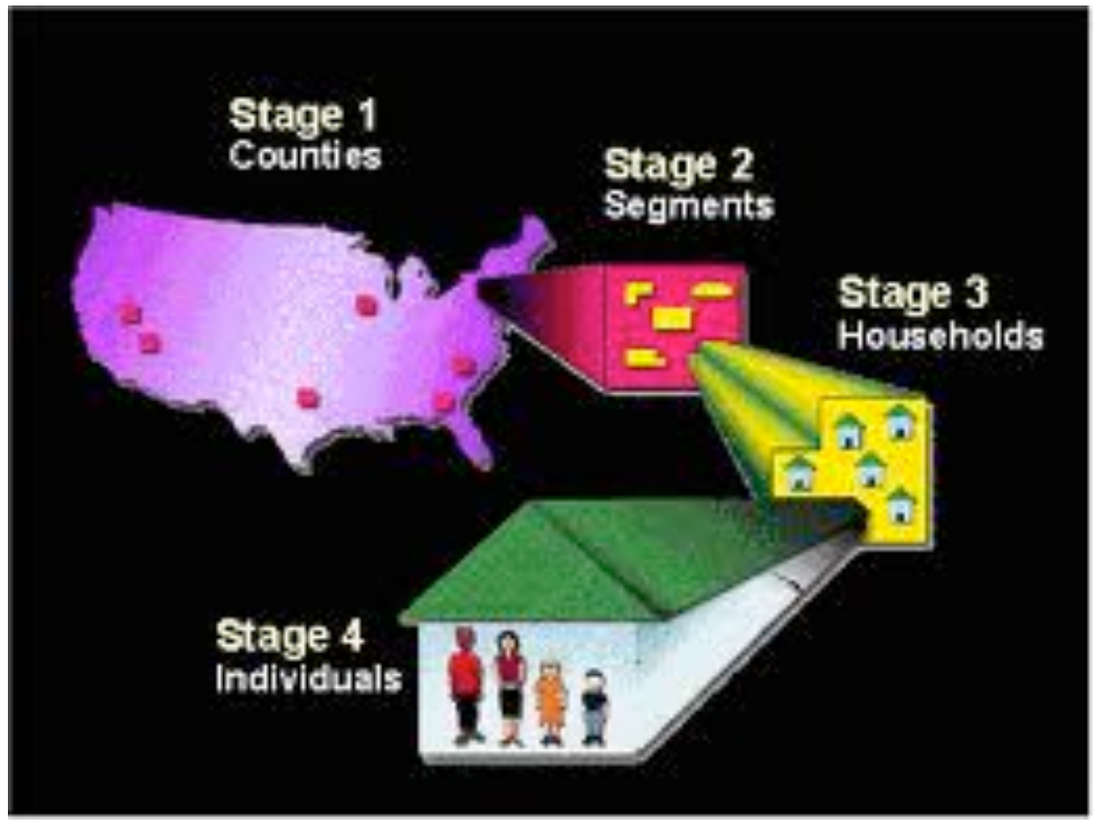
since the 1960s
now biannual: 1999 onwards
10,000 participants per survey

>250 exposures (serum + urine)

>85 quantitative clinical traits (e.g., serum glucose, lipids, body mass index)

Death index linkage (cause of death)





Ready to analyze! N=41K with >1000 variables
(let us know; we can give you a DOI)

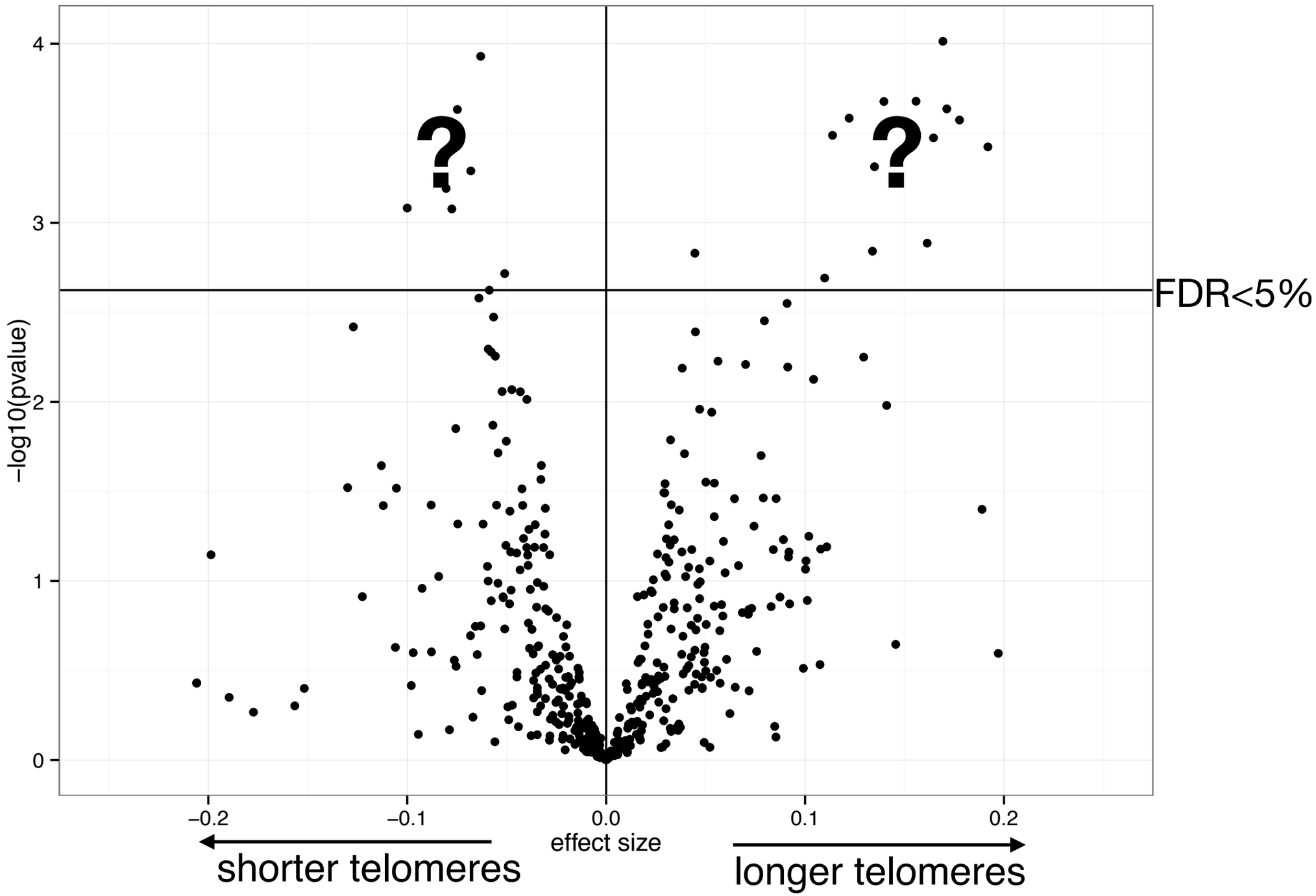
in review

13 ***EWAS***-related manuscripts

preterm birth
type 2 diabetes
type 2 diabetes genetics
lipids
blood pressure
income
mortality
telomere length
methodology (5)

http://bit.ly/ewas_nhanes

Associations in ***Telomere Length***:
Can you identify the associations in this graph?



median N=3000; N range: 300-7000

IJE, 2016

Associations in ***Telomere Length***:
Can you identify the associations in this graph?

Nam will show you how!

http://bit.ly/exposome-analytics-course

Please let us know if you are using the resources
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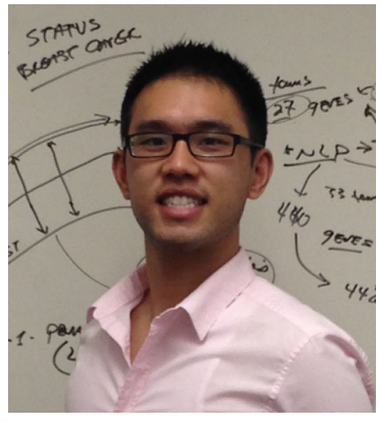

@nampho2

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Jenn Grandfield
Michal Preminger

Stanford
John PA Ioannidis

Gary Miller
Kristine Dennis

NIEHS National Institute of Environmental Health Sciences

NIH Common Fund
Big Data to Knowledge

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Agilent Technologies

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Chirag J Patel
chirag@hms.harvard.edu
@chiragjp
www.chiragjpgroup.org