

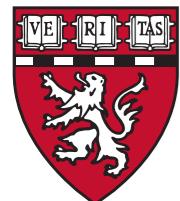
# Data analytics to enable ***X-wide Association Studies (XWASs)***

Chirag J Patel  
(with Nam Pho, Jake Chung, and Arjun Manrai)

ISEE pre-conference tutorial, part 1

Ottawa, Canada

8/26/18



HARVARD  
MEDICAL SCHOOL

DEPARTMENT OF  
Biomedical Informatics

[chirag@hms.harvard.edu](mailto:chirag@hms.harvard.edu)  
 @chiragjp  
[www.chiragjpgroup.org](http://www.chiragjpgroup.org)

# **XWAS tutorial in R markdown**

**(R code)**

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

**Materials for teaching and demonstration**

# Resources Index (for today's session)

**<http://bit.ly/xwas> with nhanes**

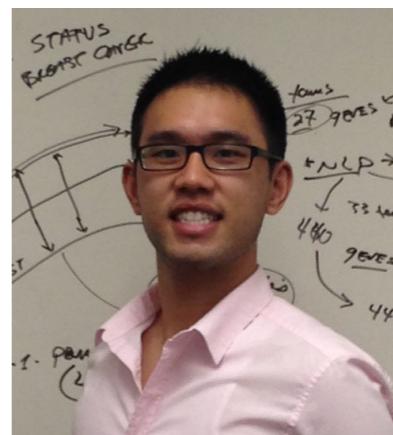
Please let us know if you are using the resources  
(or provide feedback)!

**Chirag**



  @chiragjp

**Nam**



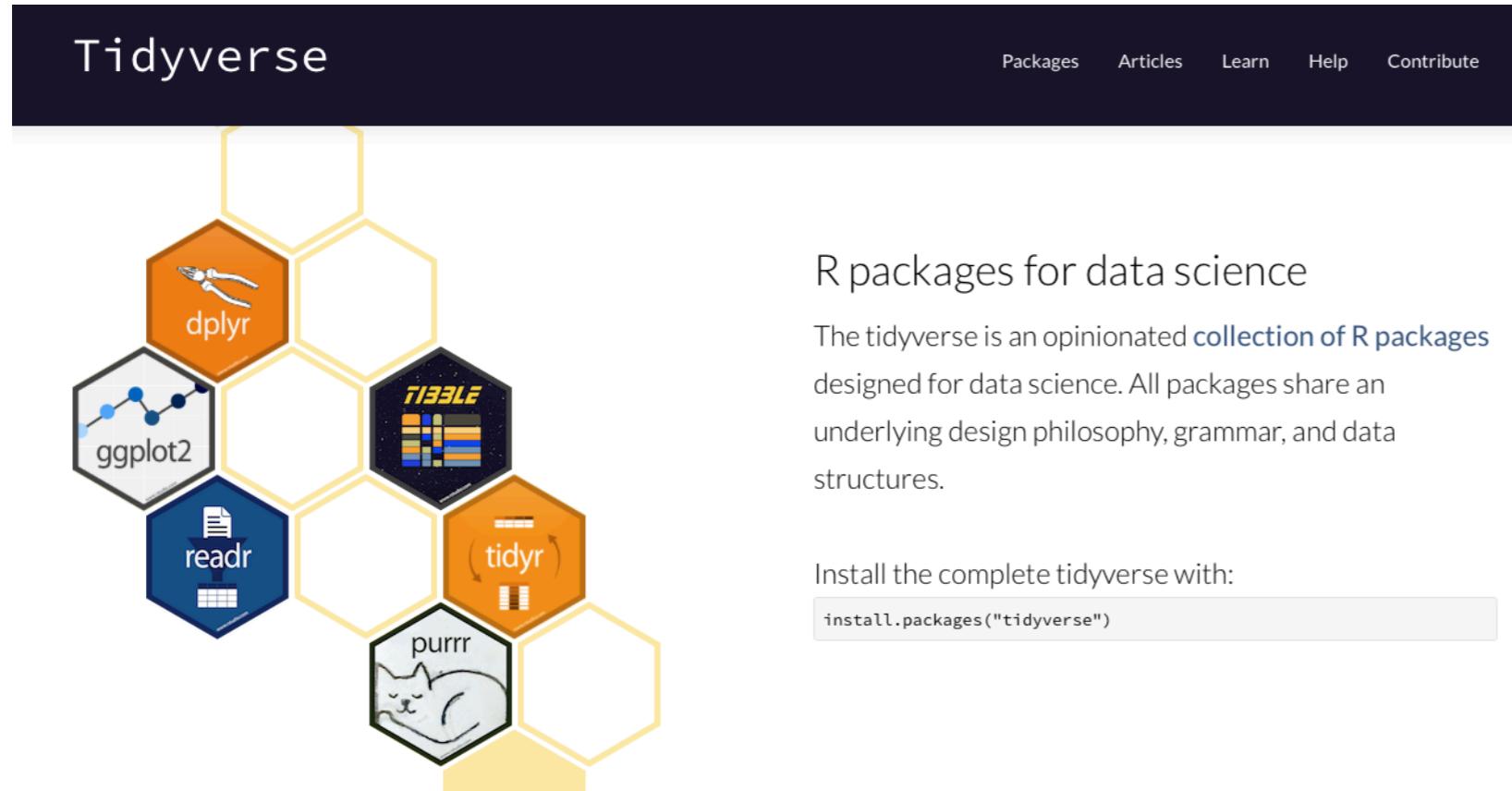
  @nampho2

first...

learn ***RStudio***, the ***tidyverse***, and ***github***  
... practice ***regression methods!***

# Intro to Data Science: *Integrating Genomes, Exposomes, and Phenomes*

## Syllabus, references and readings



Tidyverse

Packages Articles Learn Help Contribute

R packages for data science

The tidyverse is an opinionated [collection of R packages](#) designed for data science. All packages share an underlying design philosophy, grammar, and data structures.

Install the complete tidyverse with:

```
install.packages("tidyverse")
```

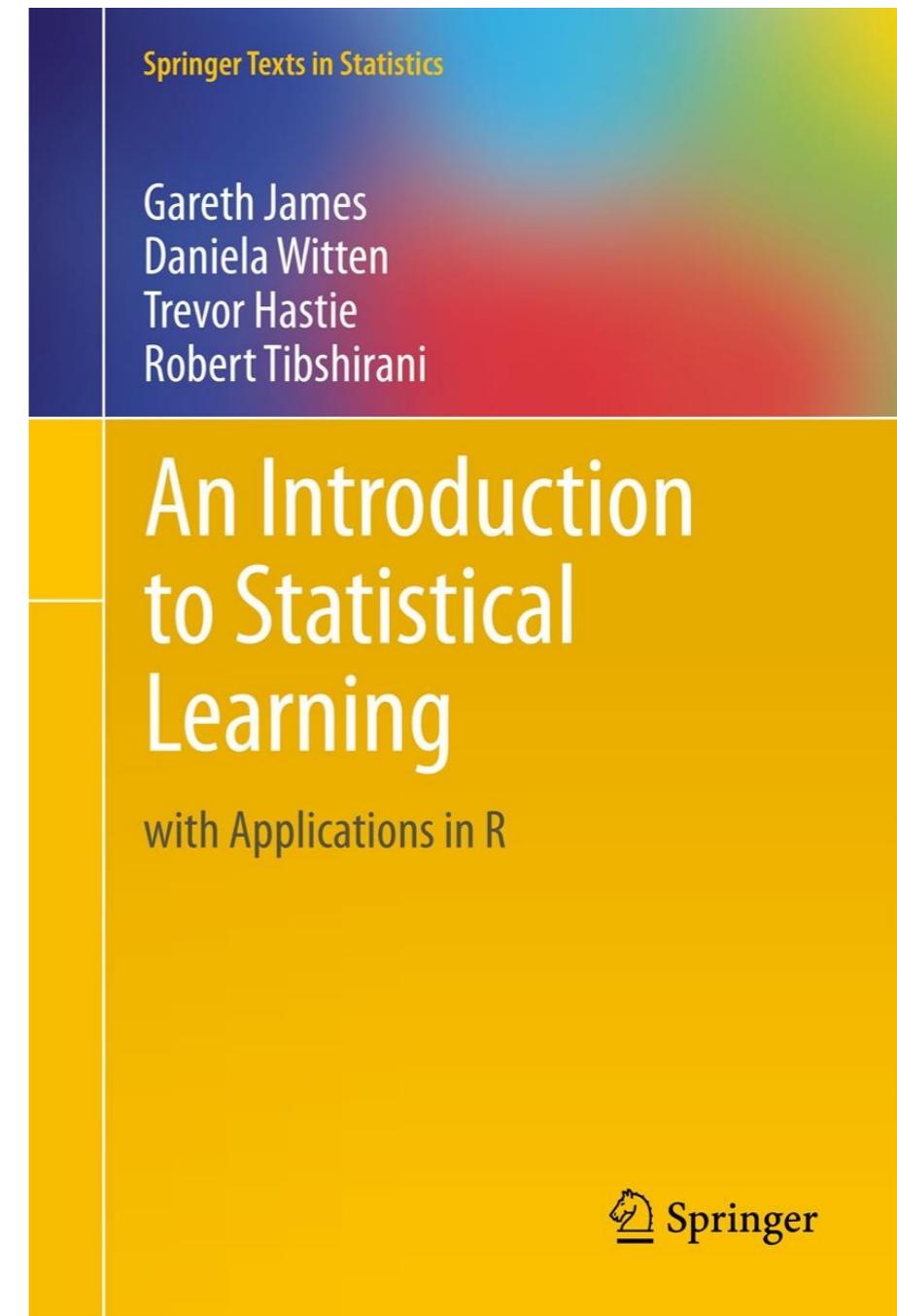
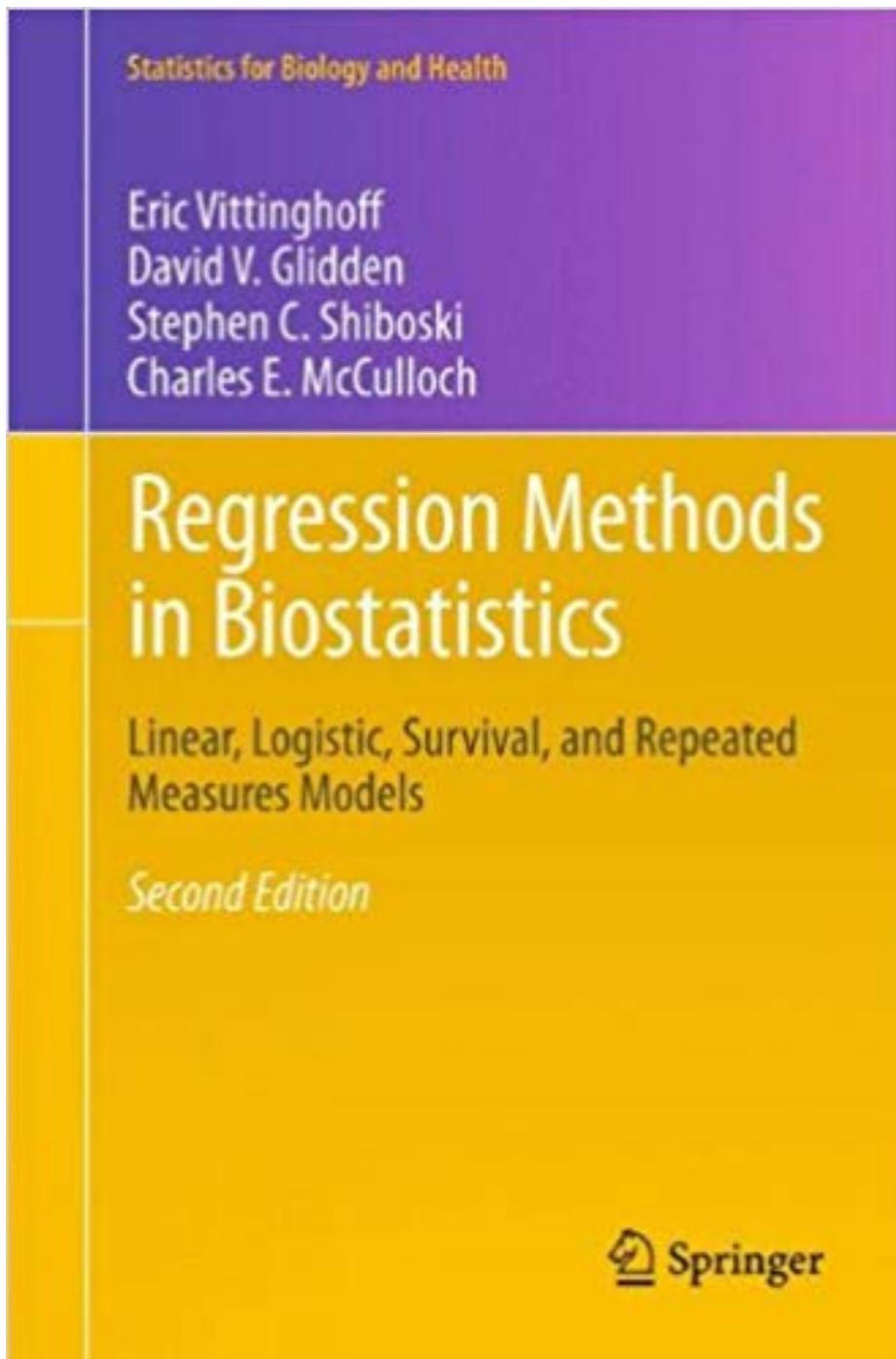


Hadley Wickham  
*Studio; tidyverse; ggplot; dplyr*

~90% (or more) of data science effort in ***processing*** – learn to do it efficiently, reproducibly, and quickly!

# Intro to Data Science: *Integrating Genomes, Exposomes, and Phenomes*

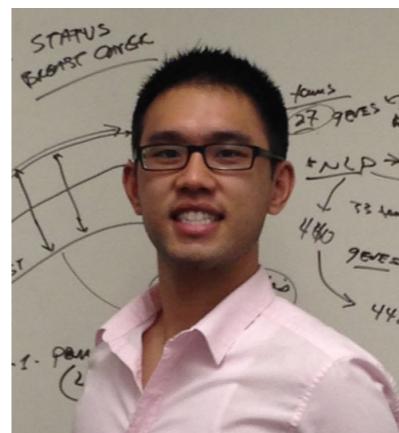
## Syllabus, references and readings



**<http://bit.ly/CORREXC>**

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

**Nam Pho**



  @nampho2

Or me:   @chiragjp

**Arjun Manrai**



 @manrai

**Jake Chung**



 @jakemk

*Real quick:*  
What is the *exposome*? What is the *phenome*?

## ***exposome***

### internal

lead (serum)

nutrients (serum)

infection (urine)

*metabolome*

### external

geography

air pollution

income

## ***phenome***

### function

expression

telomeres

*metabolome*

### diseases

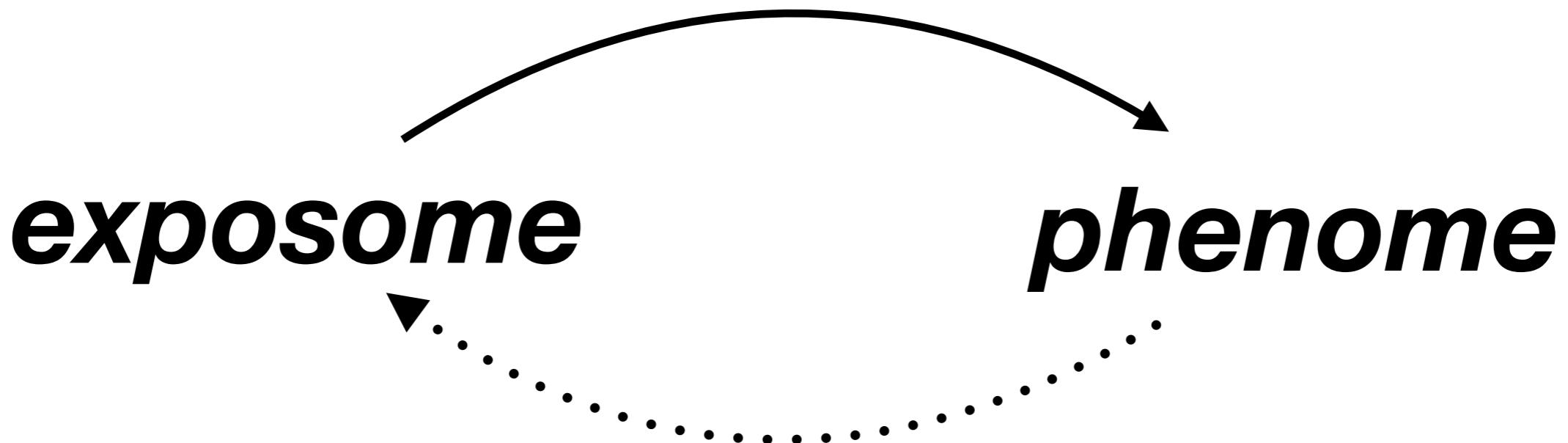
diabetes

cancer

heart disease

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

*...and vice versa?*

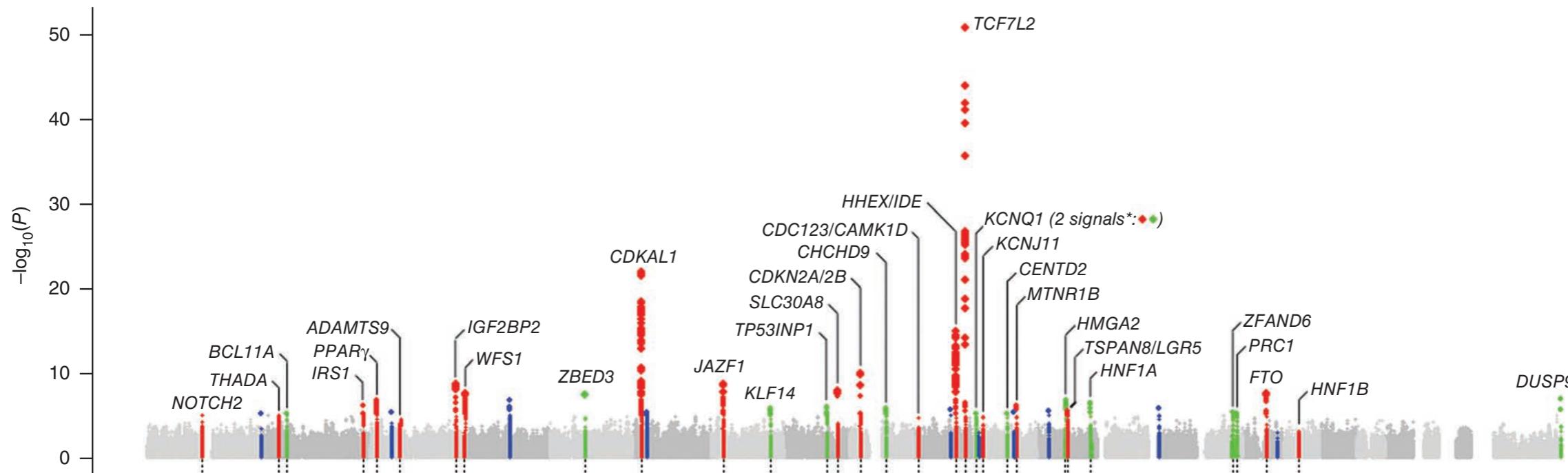


Analytic tools and big data infrastructure required to associate *exposome* with *phenome*!

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



# **Computational 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...***

But genotypes are static and have little correlation –

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

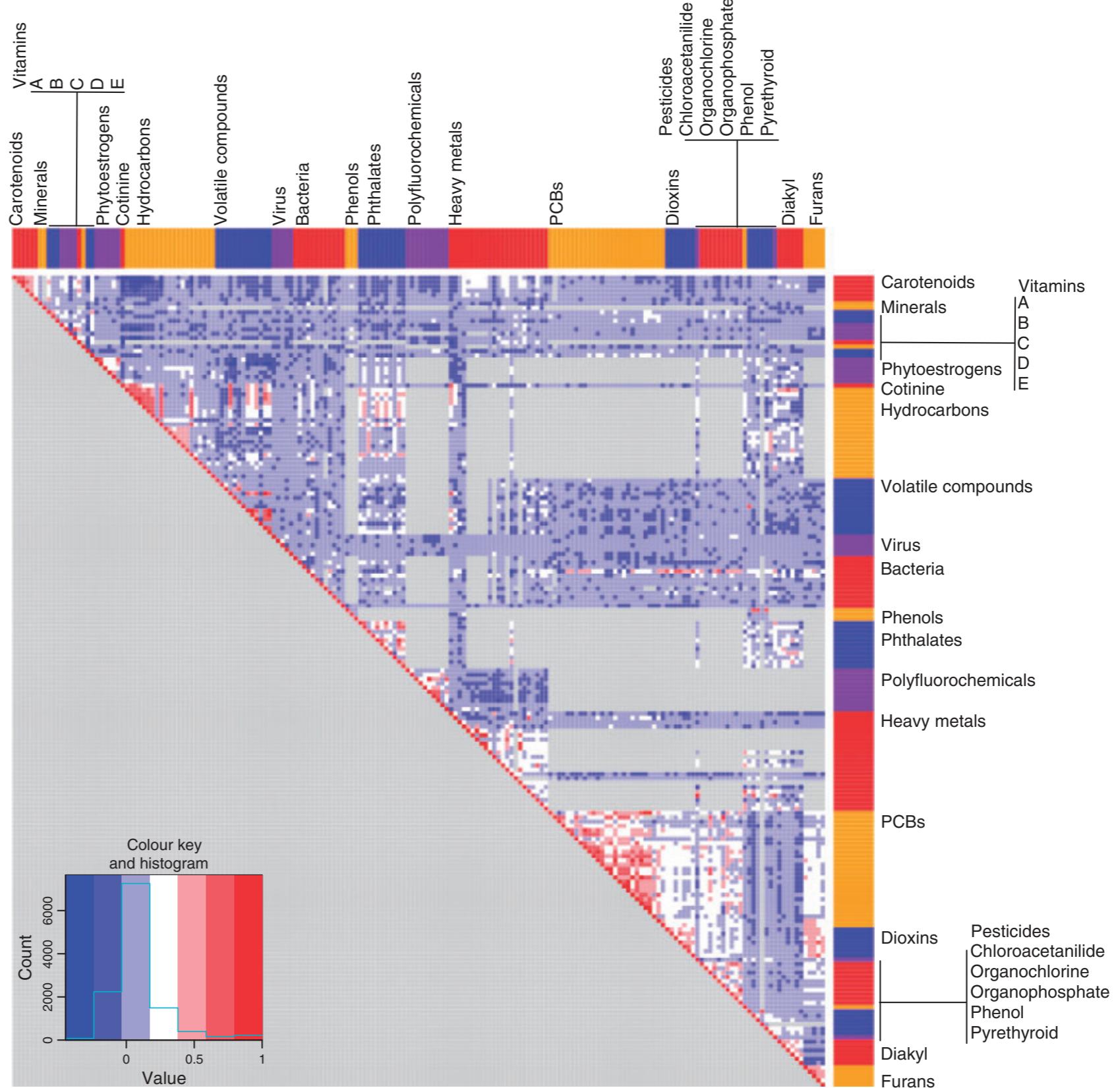
(but we will get started today!)

Dense correlational web of the exposome leads  
to complications in determining:

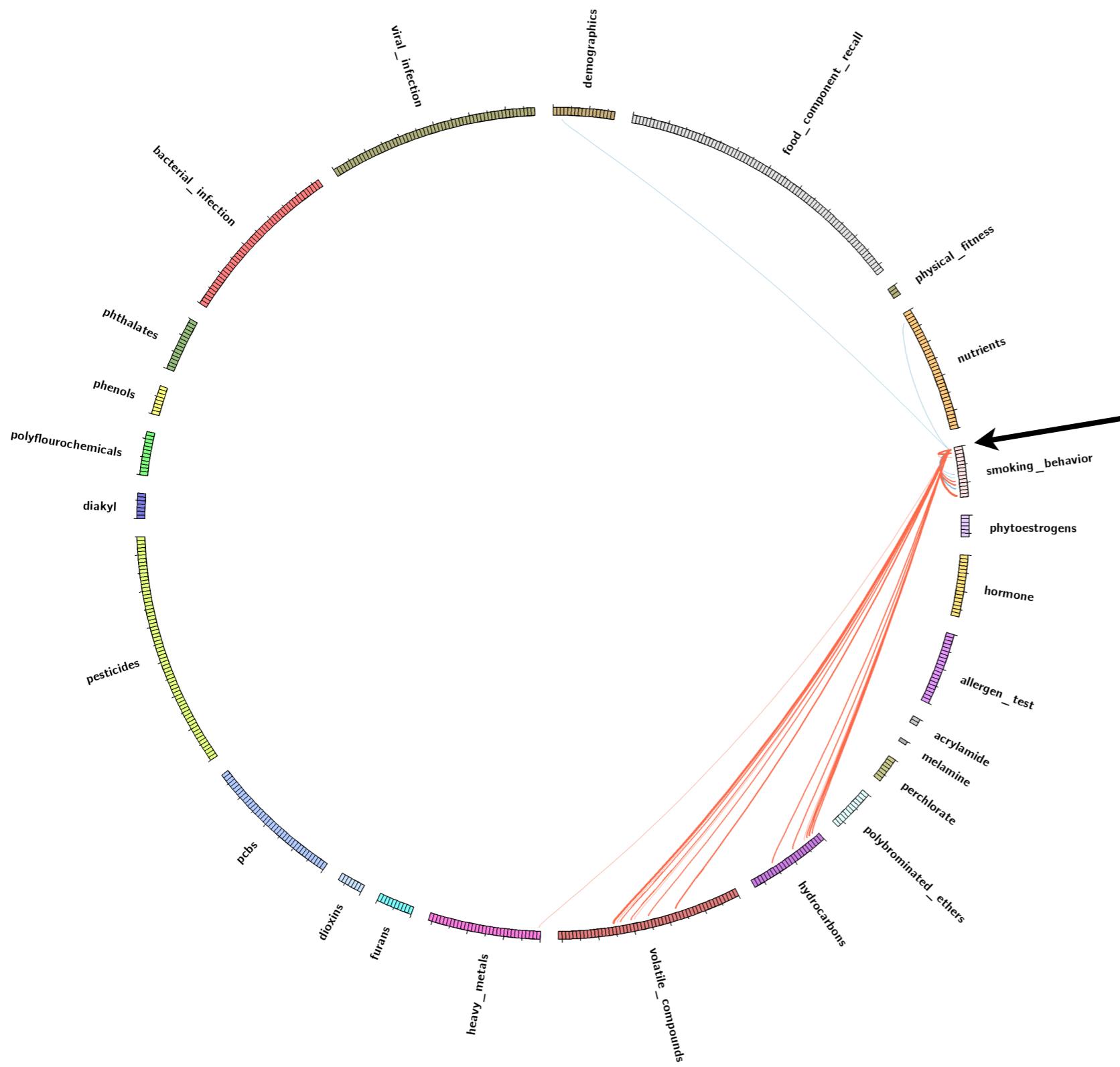
*what causes what?*

*the influence of confounding bias?*

***how many environmental factors are part of the exposome??? (10? 1000? 10000? Infinite?)***

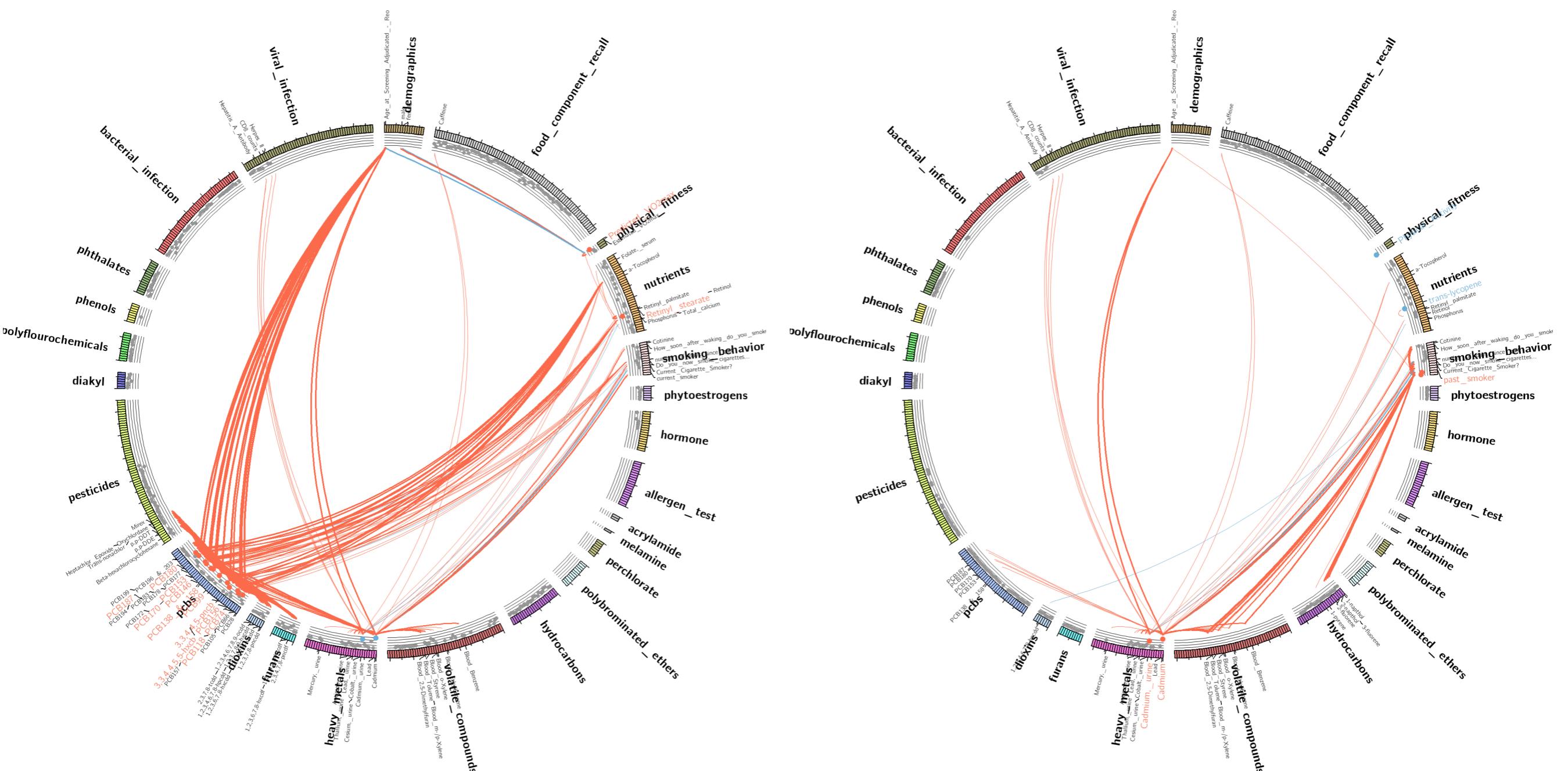


# Interdependencies of the **exosome**: Correlation globes paint a complex view of exposure



Pac Symp Biocomput. 2015  
JECH. 2015

# Interdependencies of the **exposome**: Telomeres vs. all-cause mortality

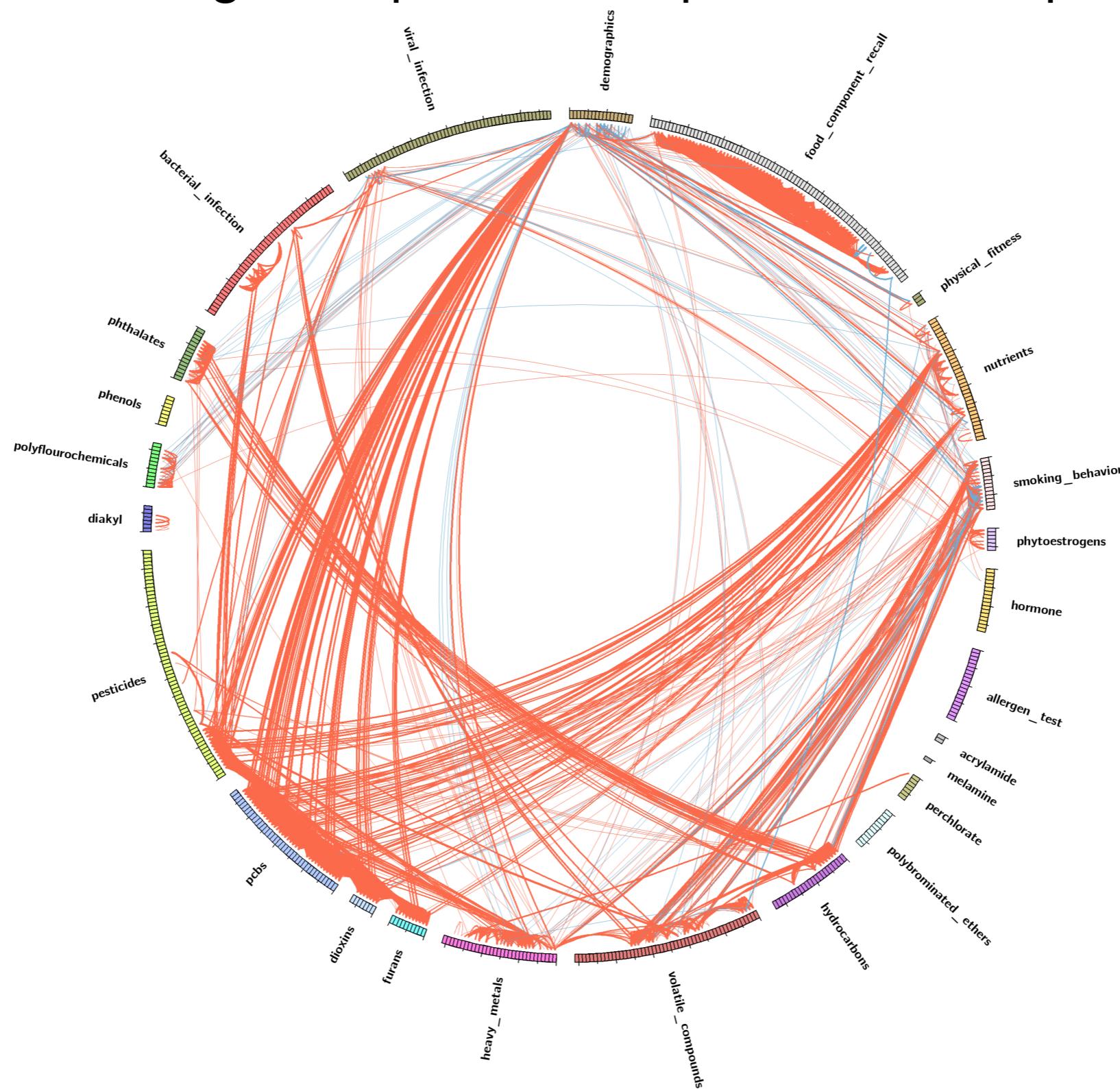


# Telomere Length

# All-cause mortality

<http://bit.ly/globebrowse>

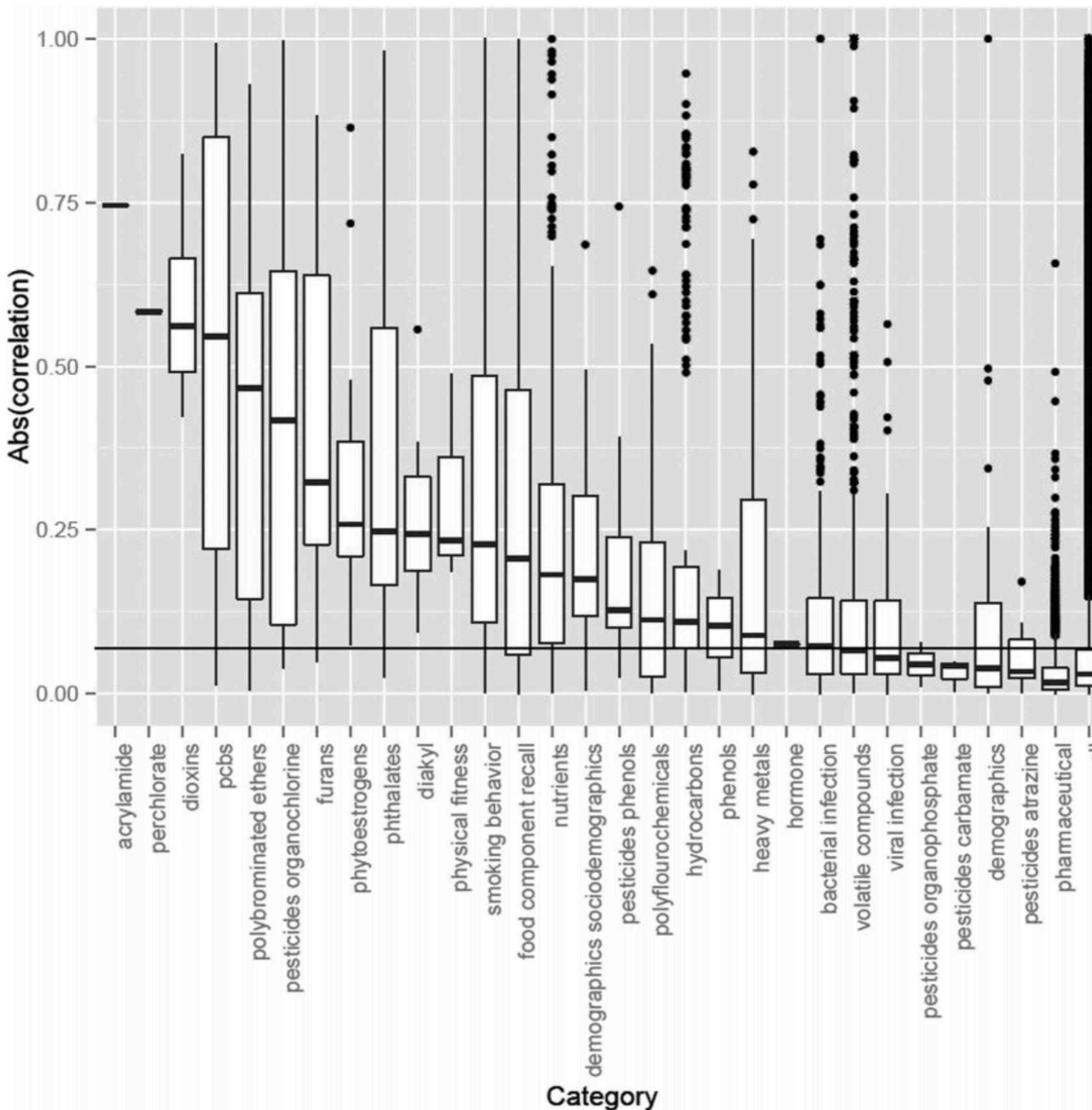
# Interdependencies of the **exposome**: Correlation globes paint a complex view of exposure



<http://bit.ly/globeweb>

Pac Symp Biocomput. 2015  
JECH. 2015

# Interdependencies of the *exposome*: Modest correlation size (Spearman/biserial $\rho < 0.5$ )



# Interdependencies of the **exposome**: Modest correlations ~ number of **effective variables (Meff)** ~= the **number of variables measured (M)**!

**Table 2** Number of variables in each of the 32 exposure, demographics or behaviour categories

| Category (measurement type)      | M   | Meff   | Mdiff | p Value |
|----------------------------------|-----|--------|-------|---------|
| Polychlorinated biphenyls (s)    | 38  | 23.79  | 14.21 | 0.002   |
| Dioxins (s)                      | 7   | 4.90   | 2.10  | 0.01    |
| Acrylamide (s)                   | 2   | 1.44   | 0.56  | 0.03    |
| Organochlorine pesticides (s)    | 13  | 9.95   | 3.05  | 0.005   |
| Polybrominated ethers (s)        | 11  | 8.47   | 2.53  | 0.006   |
| Furans (s)                       | 10  | 7.99   | 2.01  | 0.006   |
| Perchlorate (u)                  | 2   | 1.66   | 0.34  | 0.03    |
| Smoking behaviour (s/sr)         | 14  | 11.65  | 2.35  | 0.004   |
| Phthalates (u)                   | 13  | 10.85  | 2.15  | 0.005   |
| Food component recall (sr)       | 74  | 63.92  | 10.08 | 0.0008  |
| Phytoestrogens (u)               | 6   | 5.22   | 0.78  | 0.01    |
| Hydrocarbons (u)                 | 21  | 18.47  | 2.53  | 0.003   |
| Nutrients (s)                    | 29  | 26.32  | 2.68  | 0.002   |
| Volatile compounds (s)           | 38  | 34.60  | 3.40  | 0.001   |
| Physical fitness (sr*)           | 3   | 2.78   | 0.22  | 0.02    |
| Diakyl metabolites (u)           | 6   | 5.59   | 0.41  | 0.009   |
| Socioeconomics (SES) (sr)        | 9   | 8.49   | 0.51  | 0.006   |
| Demographics (sr)                | 8   | 7.55   | 0.45  | 0.007   |
| Polyflourochemicals (s)          | 12  | 11.39  | 0.61  | 0.004   |
| Phenol pesticides (u)            | 7   | 6.65   | 0.35  | 0.008   |
| Heavy metals (s/u)               | 29  | 27.68  | 1.32  | 0.002   |
| Bacterial infection (s/u)        | 33  | 32.19  | 0.81  | 0.002   |
| Viral infection (s)              | 16  | 15.72  | 0.28  | 0.003   |
| Phenols (u)                      | 3   | 2.97   | 0.03  | 0.02    |
| Atrazine-like pesticides (u)     | 6   | 5.98   | 0.02  | 0.008   |
| Hormone (s)                      | 2   | 1.99   | 0.01  | 0.03    |
| Pharmaceutical (sr)              | 107 | 106.78 | 0.22  | 0.0005  |
| Organophosphate pesticides (u)   | 4   | 4.00   | 0.00  | 0.01    |
| Carbamate pesticides (u)         | 4   | 4.00   | 0.00  | 0.01    |
| Melamine (u)                     | 1   | 1.00   | 0.00  | 0.05    |
| Chloroacetanilide pesticides (u) | 1   | 1.00   | 0.00  | 0.05    |
| Pyrethyroid pesticides (u)       | 1   | 1.00   | 0.00  | 0.05    |
| Total                            | 530 | 476.0  | 54.0  | 0.0001  |

M, number of variables in category; Meff, effective number of variables after taking into account correlation; Mdiff, difference between M and Meff; p value, indicative correlation-adjusted Bonferroni p value threshold (0.05/Meff).

\*Denotes quantitative assessment of physical activity (VO2Max) was also measured.  
s, serum; sr, self-report; u, urine.

$$M_{\text{eff}} = 1 + (M - 1) \left( 1 - \frac{\text{Var}(\lambda_{\text{obs}})}{M} \right).$$

If everything was correlated:

**Meff = 1!**

If everything was  
**not** correlated (independent):

**Meff = M!**

How large of a role does ***shared environment*** play a significant role in co-exposure of the exposome?



Possible to capture ***household*** and ***gender*** influence on variation of ***E***?

Does living together mean higher correlation?  
***E*** of individuals in the same home ***predictive*** of others?

# **Longitudinal Investigation of Fertility and the Environment (LIFE): a prospective study of couples desiring to become pregnant**

- Reproductive age (**18-40** for females; **>18** for males)
- **N=501 couples** (Michigan and Texas) in 2005-2007 living in the same home
- Data collected in couples' home
  - urine, blood, semen (at baseline and at month 1)



**Germaine Buck Louis  
(NICHD)**



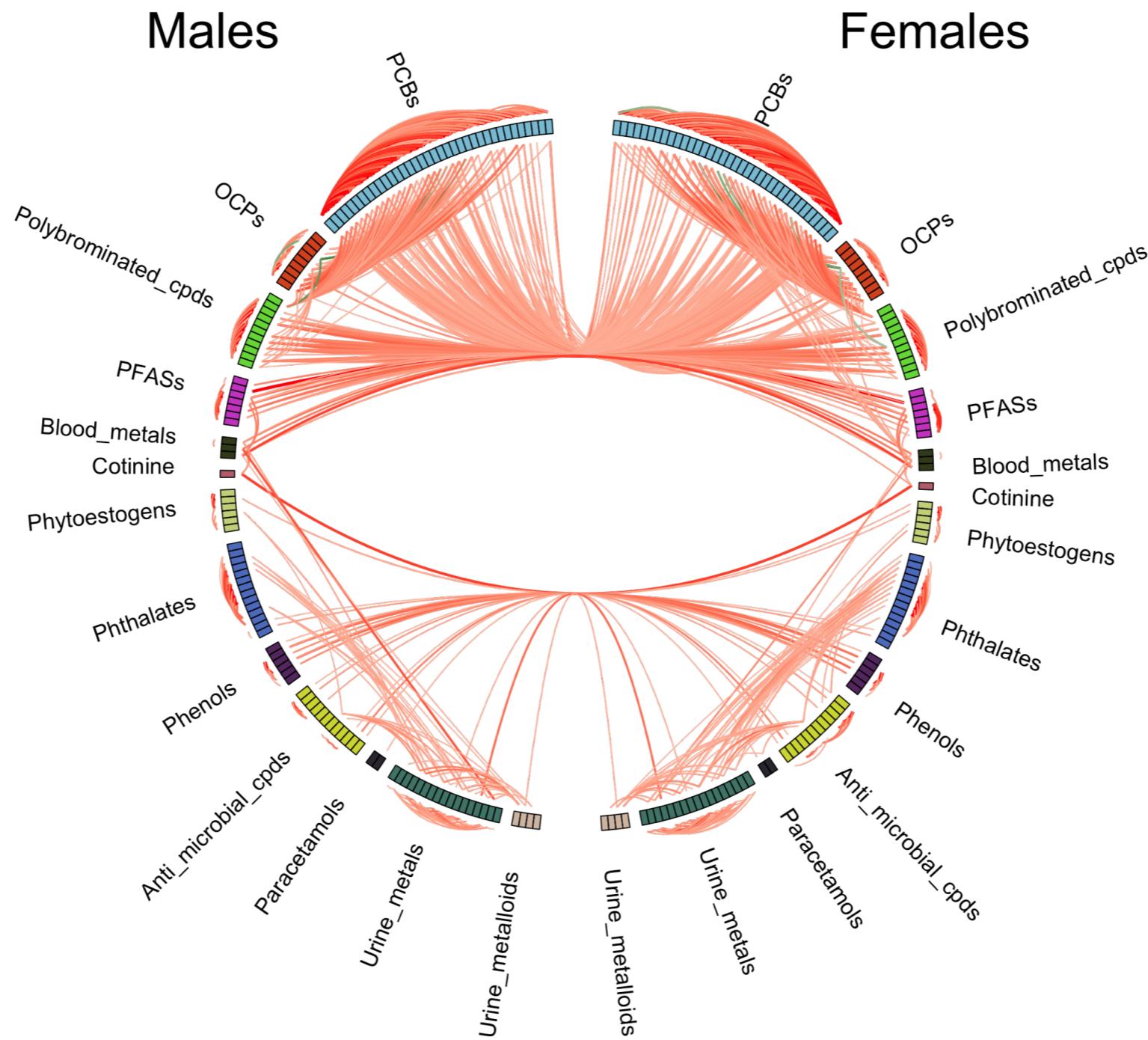
**Jake Chung**

Buck Louis et al, 2013  
Buck Louis et al, 2014  
Chung et al, ES&T 2018

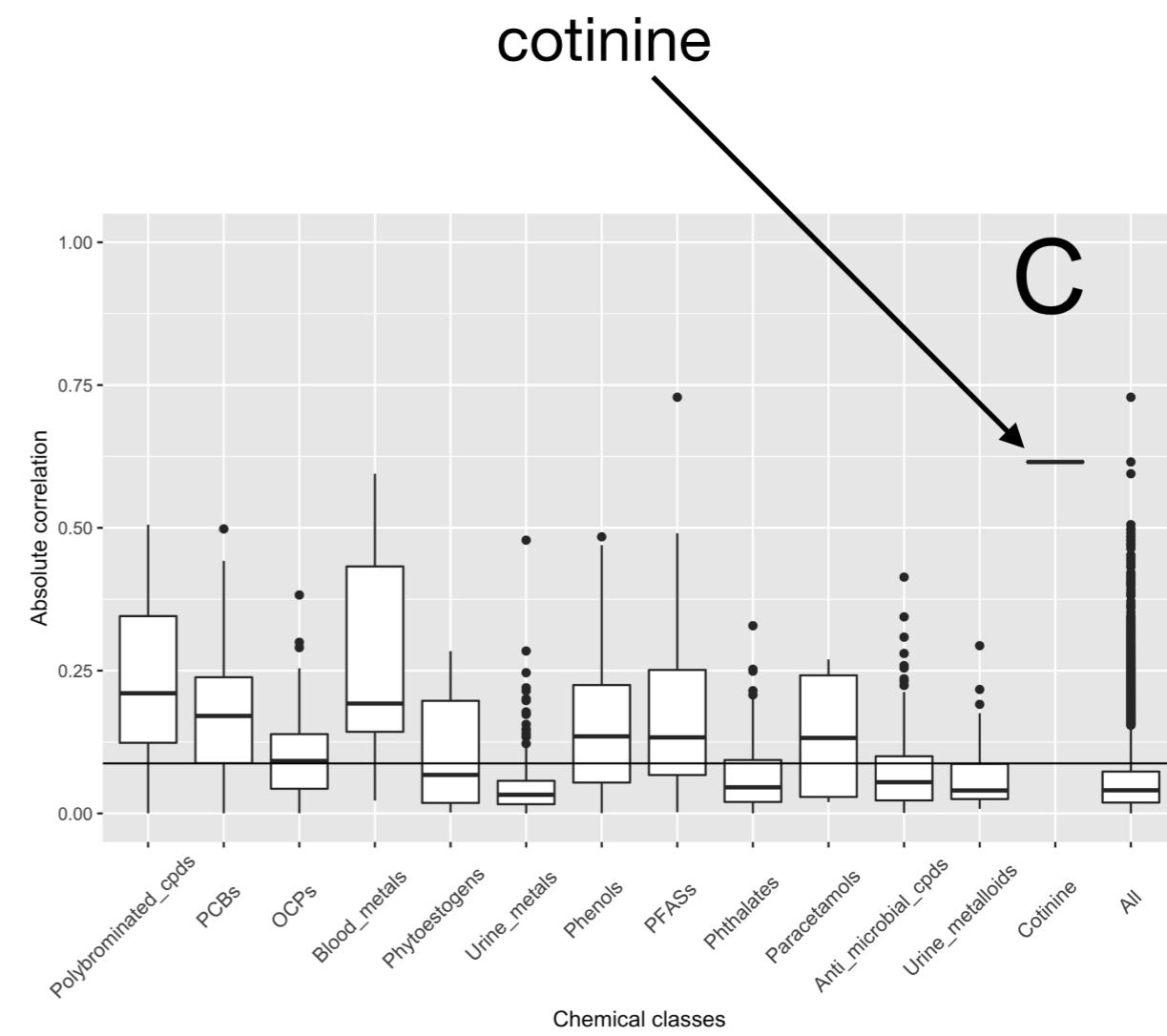
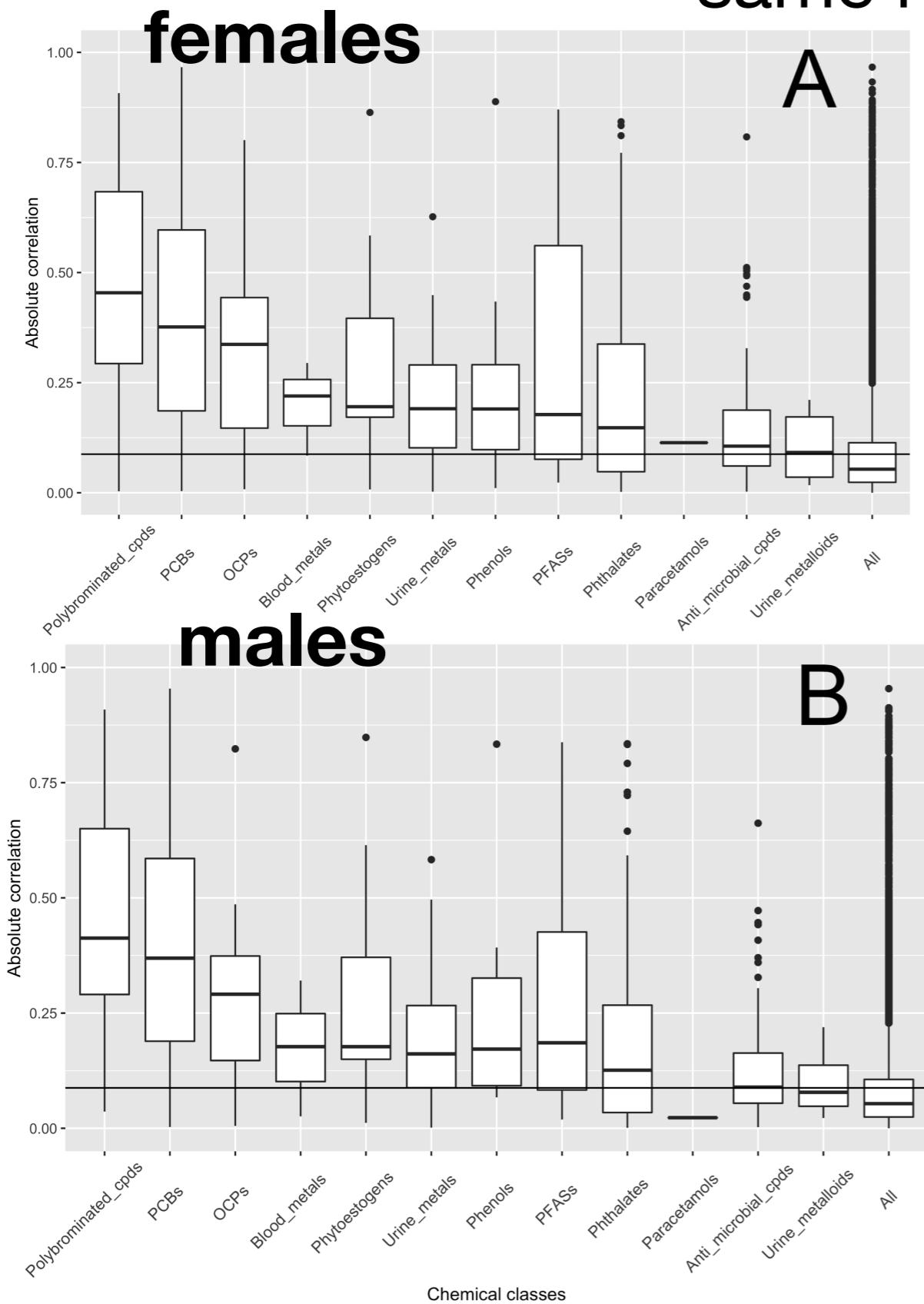
# Longitudinal Investigation of Fertility and the Environment (LIFE): a prospective study of couples with many indicators of *E!*

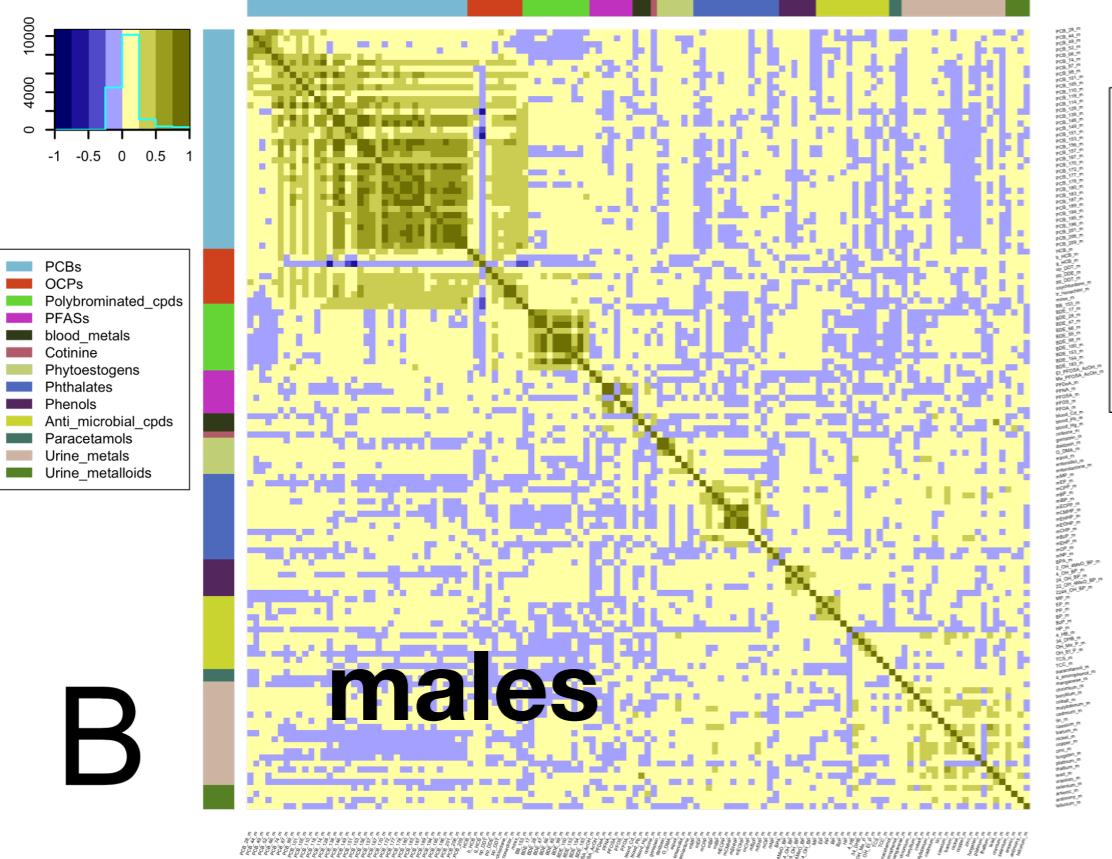
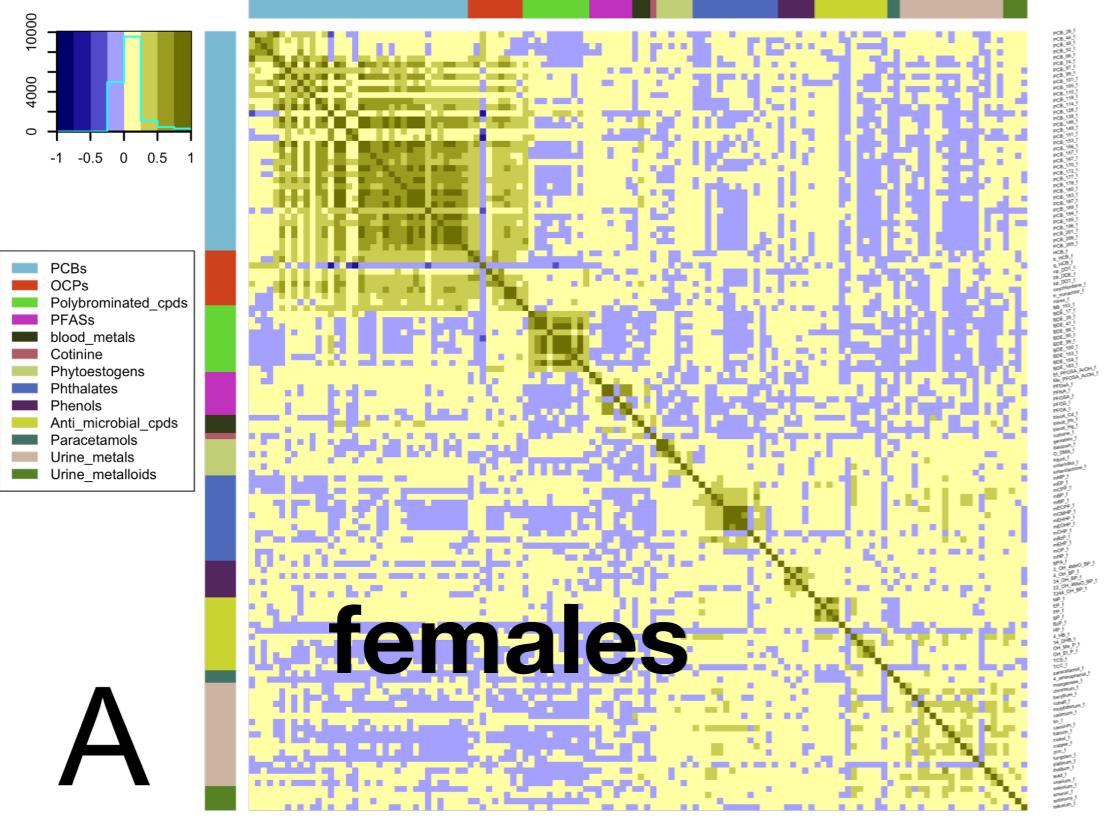
| Chemical classes                                | No. | Chemicals   |
|---|-----|---|
| <u>Serum persistent organic compounds</u>       |     |   |
| Polychlorinated biphenyls (PCBs)                | 36  | Congeners: 28, 44, 49, 52, 66, 74, 87, 99, 101, 105, 110, 114, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 201, 206, and 209   |
| Organochlorine pesticides (OCPs)                | 9   | Hexachlorobenzene (HCB), $\beta$ -hexachlorocyclohexane ( $\beta$ -HCH), $\gamma$ -hexachlorocyclohexane ( $\gamma$ -HCH), oxychlordane, <i>trans</i> -nonachlor, <i>p,p'</i> -DDT, <i>o,p'</i> -DDT, <i>p,p'</i> -DDE, and mirex   |
| Polybrominated chemicals                        | 11  | Brominated biphenyl (BB 153); brominated diphenyl ethers (BDEs) congeners: 17, 28, 47, 66, 85, 99, 100, 153, 154, and 183   |
| Polyfluoroalkyl substances (PFASs)              | 7   | 2-( <i>N</i> -ethyl-perfluorooctane sulfonamido) acetate (Et-PFOSA-AcOH), 2-( <i>N</i> -methyl-perfluorooctane sulfonamido) acetate (Me-PFOSA-AcOH), perfluorodecanoate (PFDeA), perfluorononanoate (PFNA), perfluorooctane sulfonamide (PFOSA), perfluorooctane sulfonate (PFOS), and perfluorooctanoate (PFOA)  |
| <u>Urinary non-persistent organic compounds</u> |     |   |
| Phytoestrogens                                  | 6   | Genistein, daidzein, O-desmethylangolensin, equol, enterodiol, and enterolactone  |
|   |     | Mono (3-carboxypropyl) phthalate (mCPP), monomethyl phthalate (mMP), monoethyl phthalate (mEP), mono (2-isobutyl phthalate) (mIBP), mono-n-butyl phthalate (mBP), mono (2-ethyl-5-carboxyphethyl) phthalate (mECPP), mono-[ (2-carboxymethyl) hexyl] phthalate (mCMHP), mono (2-ethyl-5-oxohexyl) phthalate (mEOHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (mEHHP), monocyclohexyl phthalate (mCHP), monobenzyl phthalate (mBzP), mono (2-ethylhexyl) phthalate (mEHP), mono-isonyl phthalate (mNP), and monooctyl phthalate (mOP). |
| Phthalate metabolites                           | 14  | Total bisphenol A (BPA); benzophenones (BPs): 4-hydroxybenzophenone (4-OH-BP), 2,4-dihydroxybenzophenone (2,4-OH-BP), 2,2',4,4'-tetrahydroxybenzophenone (2,2'4,4'-OH-BP), 2-hydroxy-4-methoxybenzophenone (2-OH-4-MeO-BP), and 2,2'-dihydroxy-4-methoxybenzophenone (2,2'-OH-4-MeO-BP)   |
| Phenols   | 6   | Triclosan (TCS) and triclocarban (TCC); parabens: methyl paraben (MP), ethyl paraben (EP), propyl paraben (PP), butyl paraben (BP), benzyl paraben (BzP), heptyl paraben (HP), 4-hydroxy benzoic acid (4-HB), 3,4-dihydroxy benzoic (3,4-DHB), methyl-protocatechuic acid (OH-Me-P), and ethyl-protocatechuic acid (OH-Et-P)  |
| Anti-microbial chemicals                        | 12  |   |
| Paracetamol & derivatives                       | 2   | Paracetamol and 4-aminophenol   |
| <u>Others</u>                                   |     |   |
| Blood metals                                    | 3   | Cadmium (Cd), lead (Pb), and mercury (Hg)   |
| Serum cotinine                                  | 1   | Cotinine  |
| Urine metals                                    | 17  | Manganese (Mn), chromium (Cr), beryllium (Be), cobalt (Co), molybdenum (Mo), cadmium (Cd), tin (Sn), caesium (Cs), barium (Ba), nickel (Ni), copper (Cu), zinc (Zn), tungsten (W), platinum (Pt), thallium (Tl), lead (Pb), and uranium (U)   |
| Urine metalloids                                | 4   | Selenium (Se), arsenic (As), antimony (Sb), and tellurium (Te)  |

Dense correlational web in **LIFE** comparable to **NHANES**:  
90% spearman correlations ranging from -0.3 to 0.3



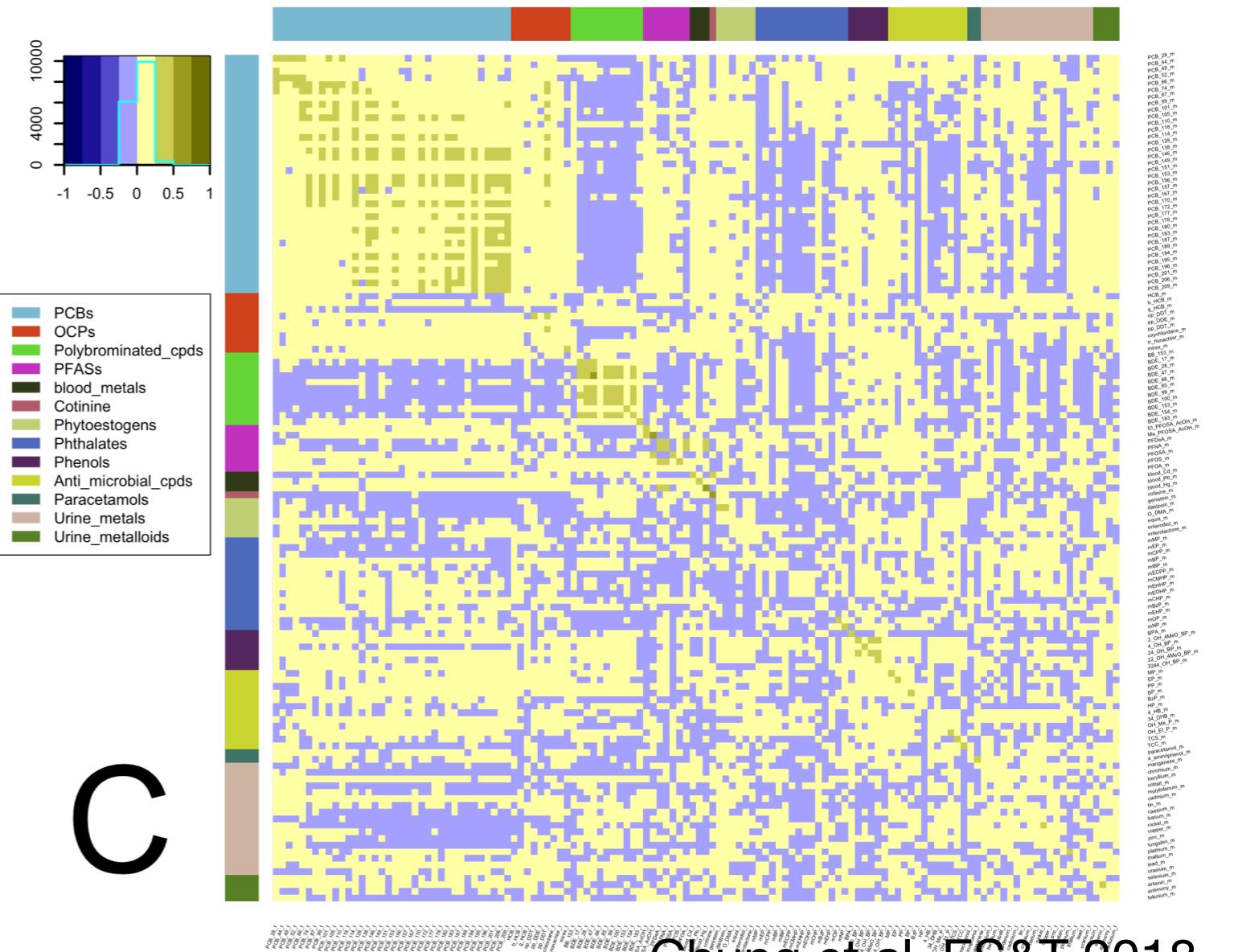
**$\text{cor}(\text{persistent } E) > \text{cor}(\text{non-persistent } E)$**   
 (but this pattern **diminishes** between couples in the  
 same household!)



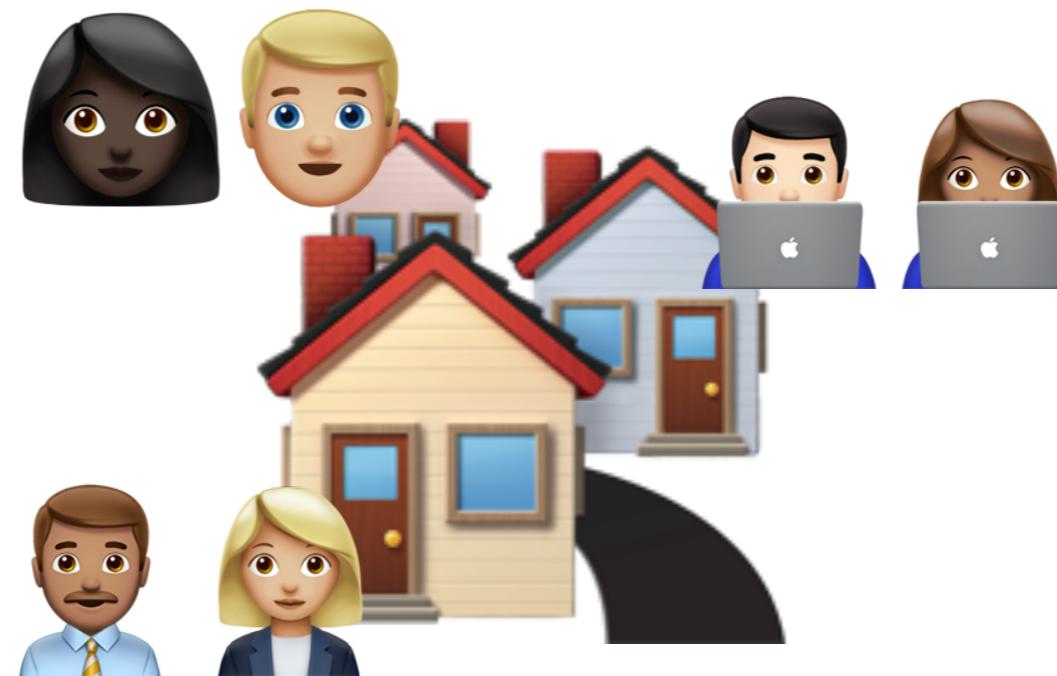


**Co-*E* patterns between females and males are *similar***

**... however:**  
**males and females *within* household weaker!**

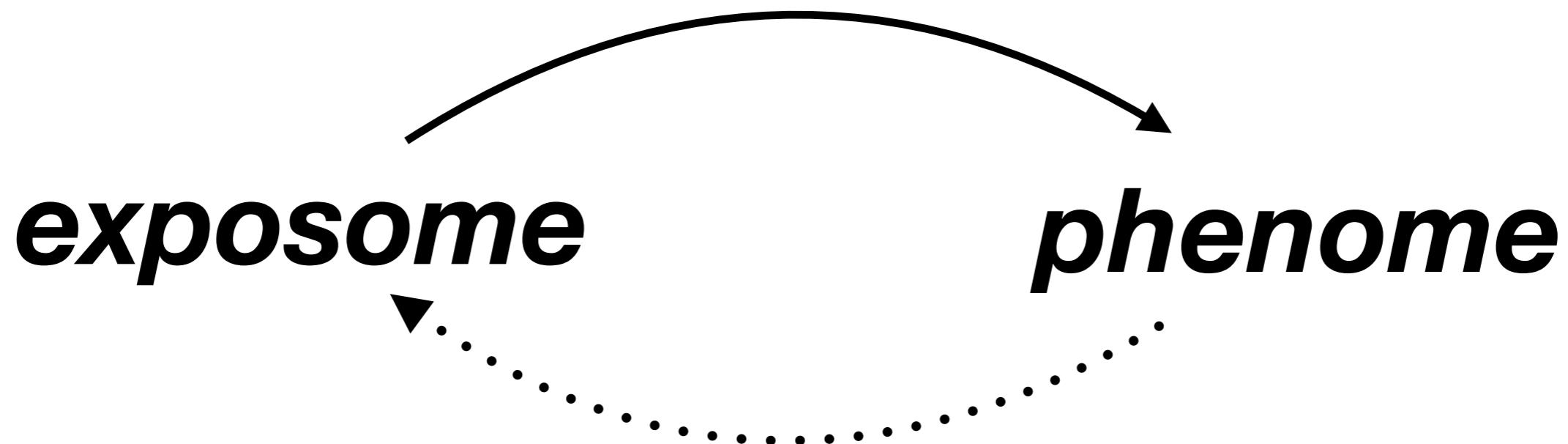


# ***Household < specific environment*** in co-occurring exposures



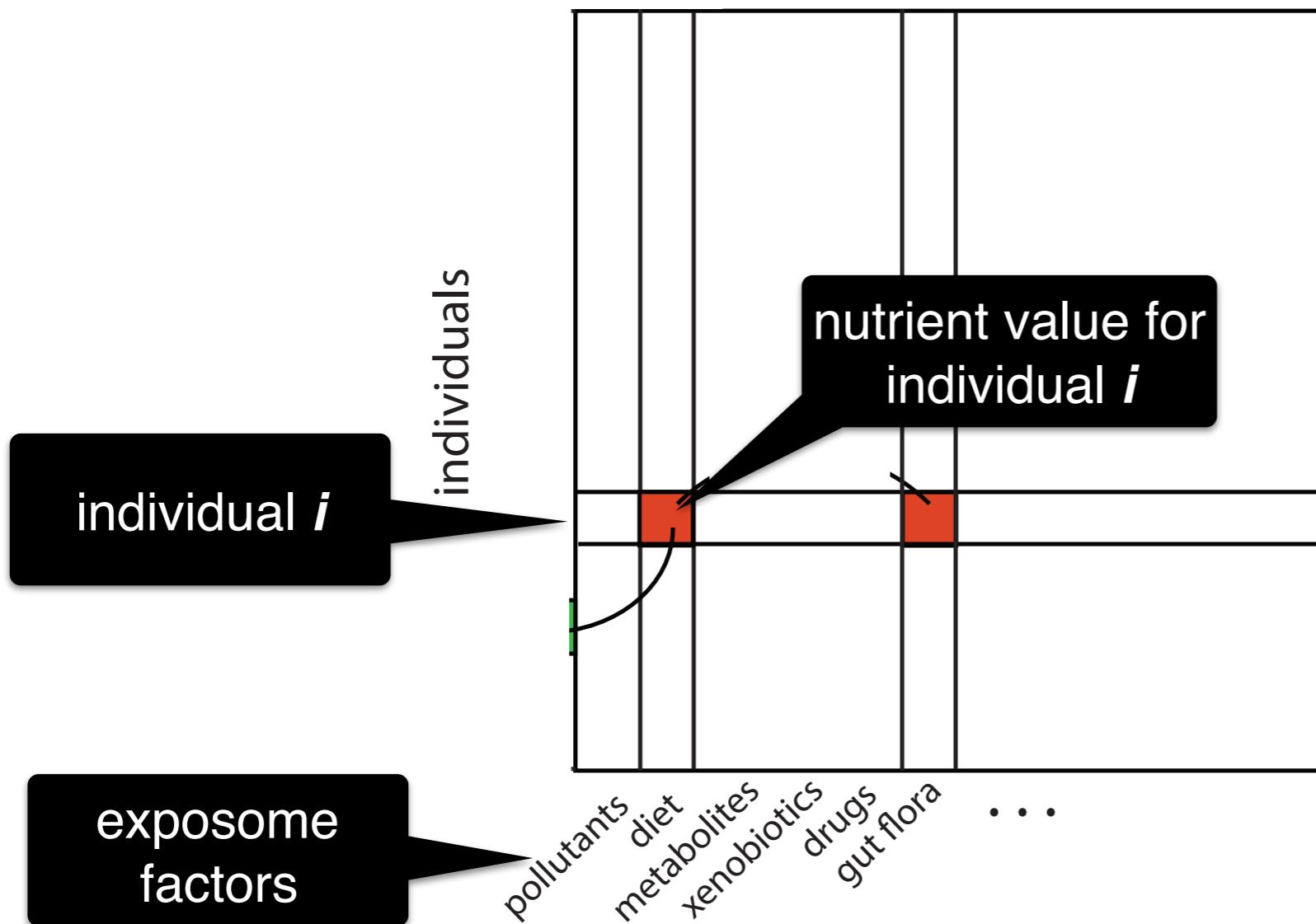
implications for **sampling, routes of exposure:**  
where do we sample? - *individuals!*

# ***X-wide Association Investigations: Correlating the exposome with the phenome***



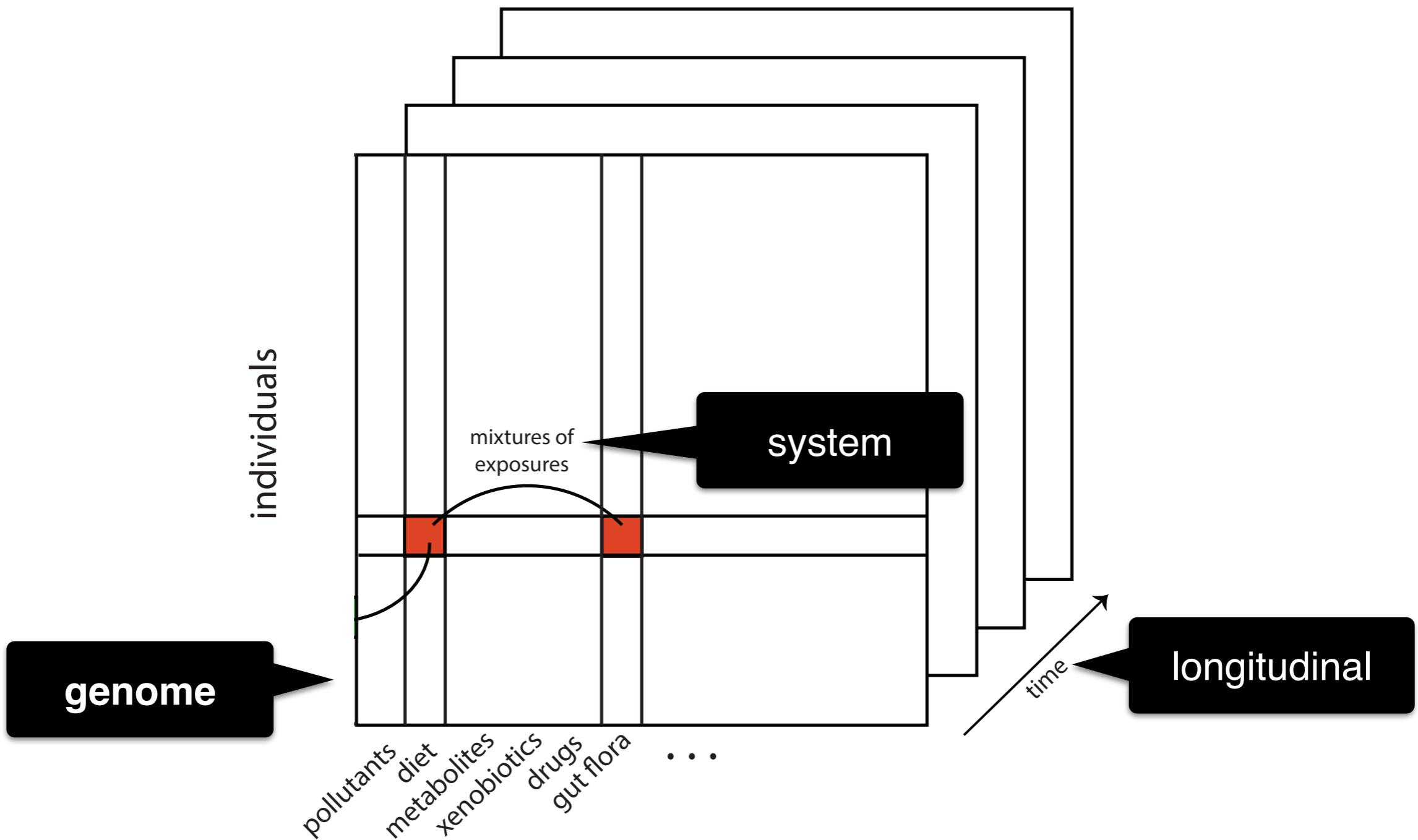
What will the ***exposome*** data structure look like?:

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



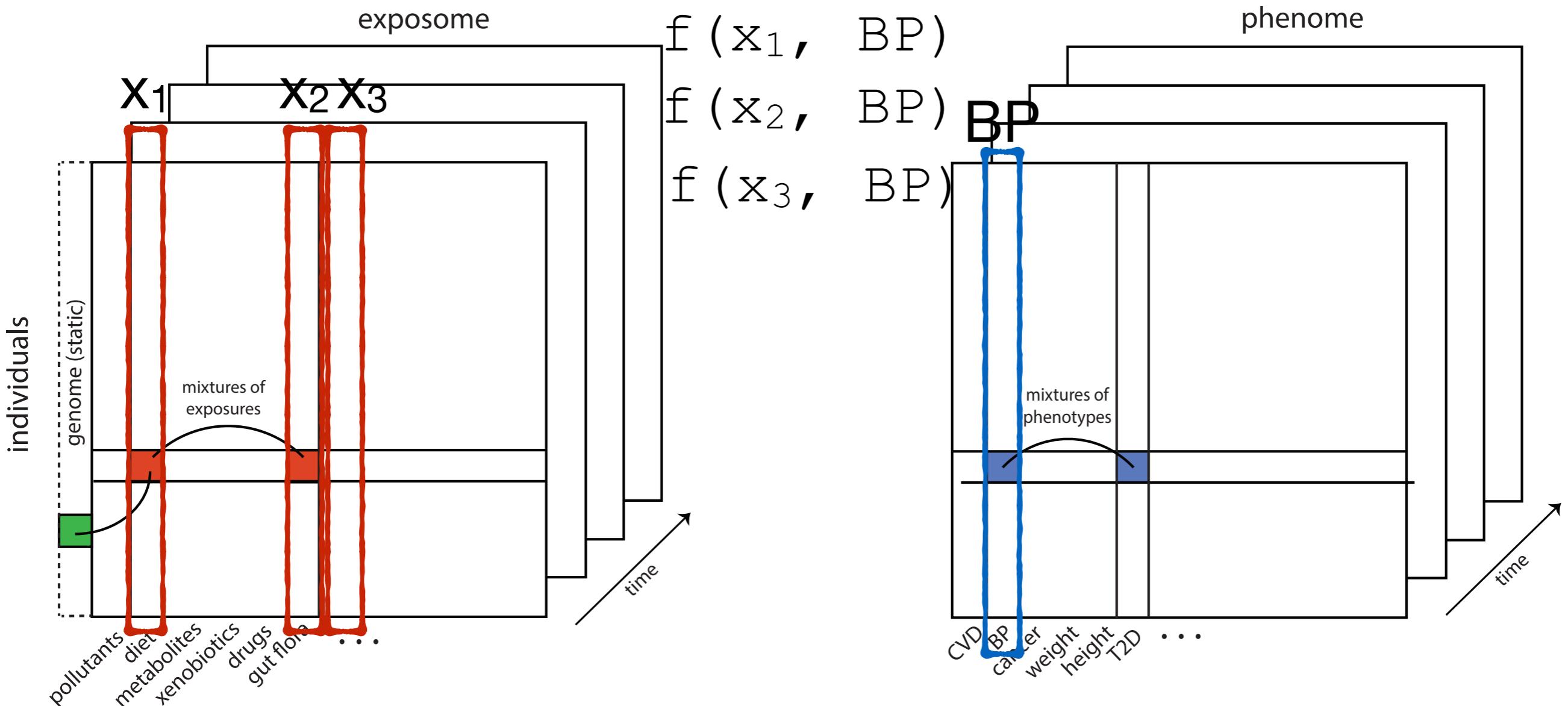
What will the ***exosome*** data structure look like?:

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



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

*Associating all of the ‘red’ with the ‘blue’*



Where  $f$  = association function  
 (regression, correlation, etc)

## ‘pseudo-code’ for implementation of an XWAS: *how would you do it?*

```
y = [blood pressure values for cohort]
association_list = empty_list()
for each x in list of exposures:
    association_test=f(x,y)
    append(association_list, association_test)

multiplicity_correct(association_list)

volcano_plot(y, x, association_list)
```

What is stored in  $y$ ?

What is stored in  $\text{association\_list}$ ?

What can  $f$  be?

What does  $\text{append}$  do?

What is the reason for  $\text{multiplicity\_correct}$ ?

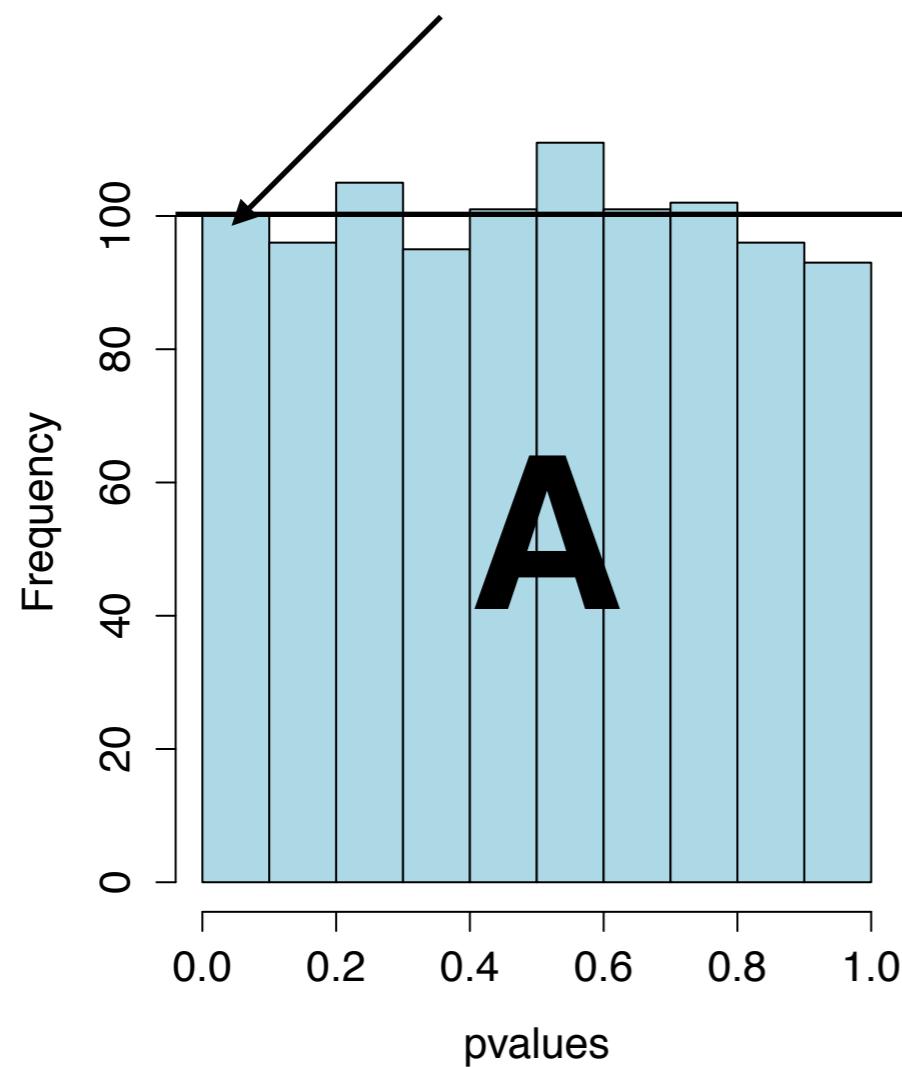
**Multiplicity:** how to determine signal from noise?  
*type 1 error (spurious findings)*

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

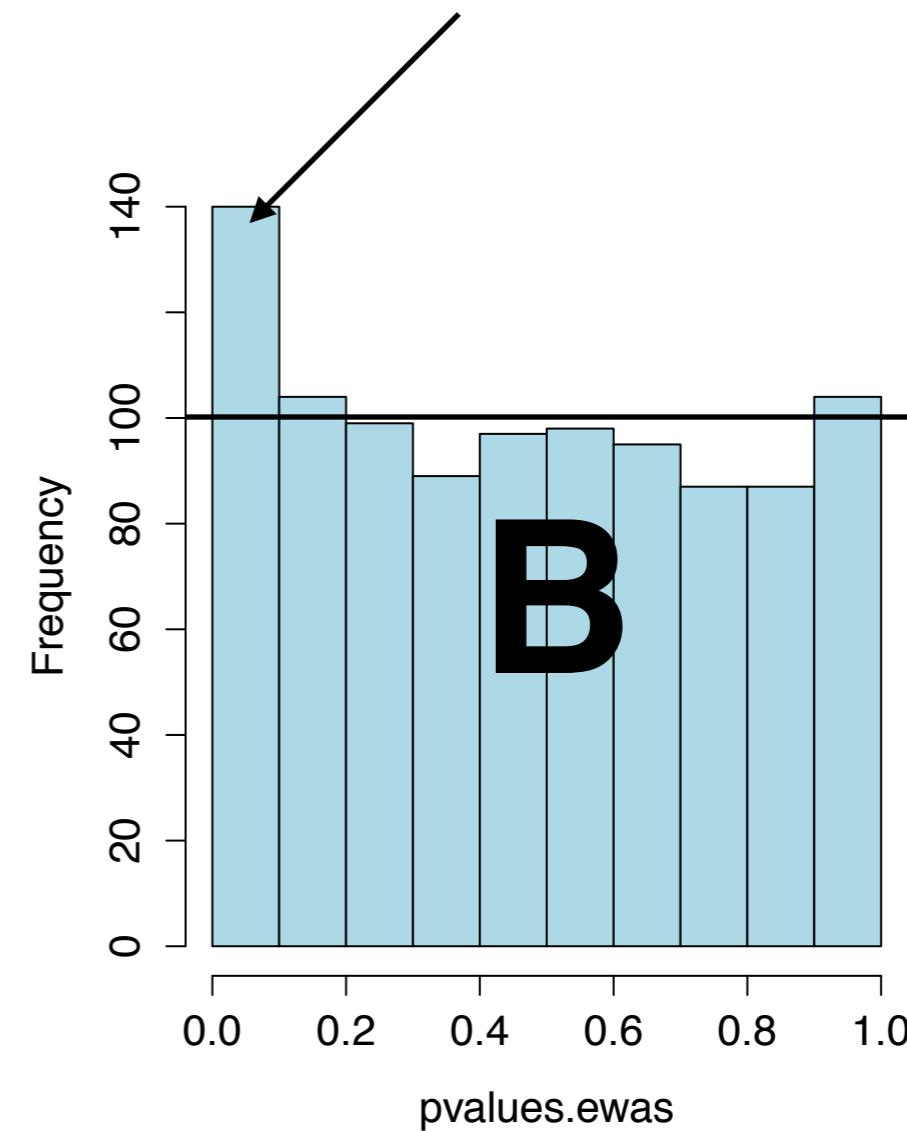
*... and there were no difference between the cases and controls...*

**...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

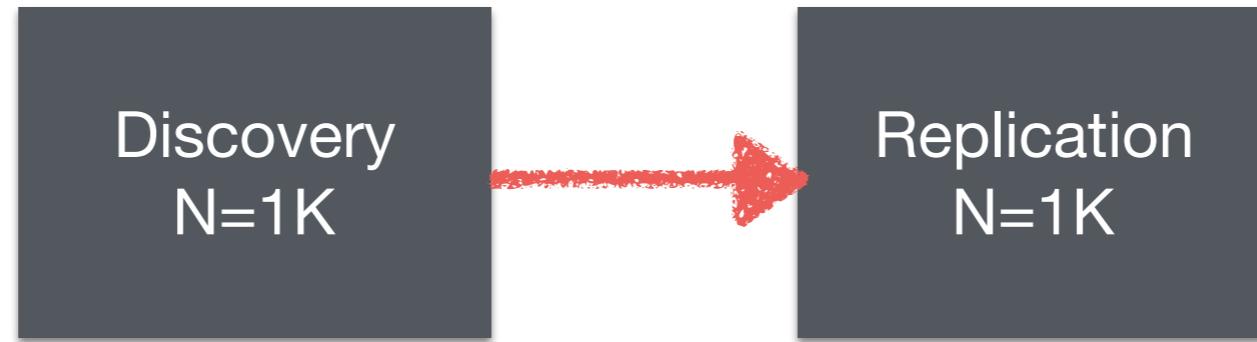


**No difference**  
(no true associations)



**5% exposures different**  
(5% true associations)

# 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

# The *false discovery rate*: A *powerful* approach for multiple hypothesis correction

*J. R. Statist. Soc. B* (1995)  
**57**, No. 1, pp. 289–300

## **Controlling the False Discovery Rate: a Practical and Powerful Approach to Multiple Testing**

By YOAV BENJAMINI† and YOSEF HOCHBERG

*Tel Aviv University, Israel*

[Received January 1993. Revised March 1994]

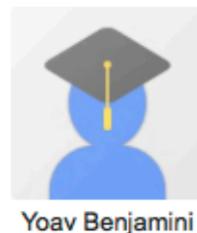
### SUMMARY

The common approach to the multiplicity problem calls for controlling the familywise error rate (FWER). This approach, though, has faults, and we point out a few. A different approach to problems of multiple significance testing is presented. It calls for controlling the expected proportion of falsely rejected hypotheses – the false discovery rate. This error rate is equivalent to the FWER when all hypotheses are true but is smaller otherwise. Therefore, in problems where the control of the false discovery rate rather than that of the FWER is desired, there is potential for a gain in power. A simple sequential Bonferroni-type procedure is proved to control the false discovery rate for independent test statistics, and a simulation study shows that the gain in power is substantial. The use of the new procedure and the appropriateness of the criterion are illustrated with examples.

*Keywords:* BONFERRONI-TYPE PROCEDURES; FAMILYWISE ERROR RATE; MULTIPLE-COMPARISON PROCEDURES; *p*-VALUES

- “**powerful**”: *p*-value threshold less stringent than Bonferroni
- an estimate of frequency of **false discoveries** at a given threshold!

# The *false discovery rate*: A *powerful* approach for multiple hypothesis correction



Yoav Benjamini

Controlling the false discovery rate: a practical and powerful approach to multiple testing

|                  |  |
|------------------|--|
| Authors          | Yoav Benjamini, Yosef Hochberg   |
| Publication date | 1995/1/1   |
| Journal          | Journal of the royal statistical society. Series B (Methodological)  |
| Pages            | 289-300  |
| Publisher        | Blackwell Publishers   |
| Description      | The common approach to the multiplicity problem calls for controlling the familywise error rate (FWER). This approach, though, has faults, and we point out a few. A different approach to problems of multiple significance testing is presented. It calls for controlling the expected proportion of falsely rejected hypotheses—the false discovery rate. This error rate is equivalent to the FWER when all hypotheses are true but is smaller otherwise. Therefore, in problems where the control of the false discovery rate rather than that of the FWER is ... |
| Total citations  | Cited by 37060   |



Scholar articles [Controlling the false discovery rate: a practical and powerful approach to multiple testing](#)  
Y Benjamini, Y Hochberg - Journal of the royal statistical society. Series B ( ..., 1995  
[Cited by 37060 - Related articles - All 47 versions](#)

- “**powerful**”: pvalue threshold less stringent than Bonferroni
- an estimate of frequency of **false discoveries** at a given threshold!

# The *false discovery rate*: A *powerful* approach for multiple hypothesis correction

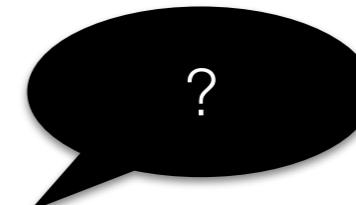
TABLE 1  
*Number of errors committed when testing  $m$  null hypotheses*

|                          | <i>Declared<br/>non-significant</i> | <i>Declared<br/>significant</i> | <i>Total</i> |
|--------------------------|-------------------------------------|---------------------------------|--------------|
| True null hypotheses     | $U$                                 | $V$                             | $m_0$        |
| Non-true null hypotheses | $T$                                 | $S$                             | $m - m_0$    |
|                          | $m - R$                             | $R$                             | $m$          |

$$\text{FDR} = V / R$$

- “**powerful**”: pvalue threshold less stringent than Bonferroni
- an estimate of frequency of **false discoveries** at a given threshold!

# How can I compute the *False Discovery Rate*?

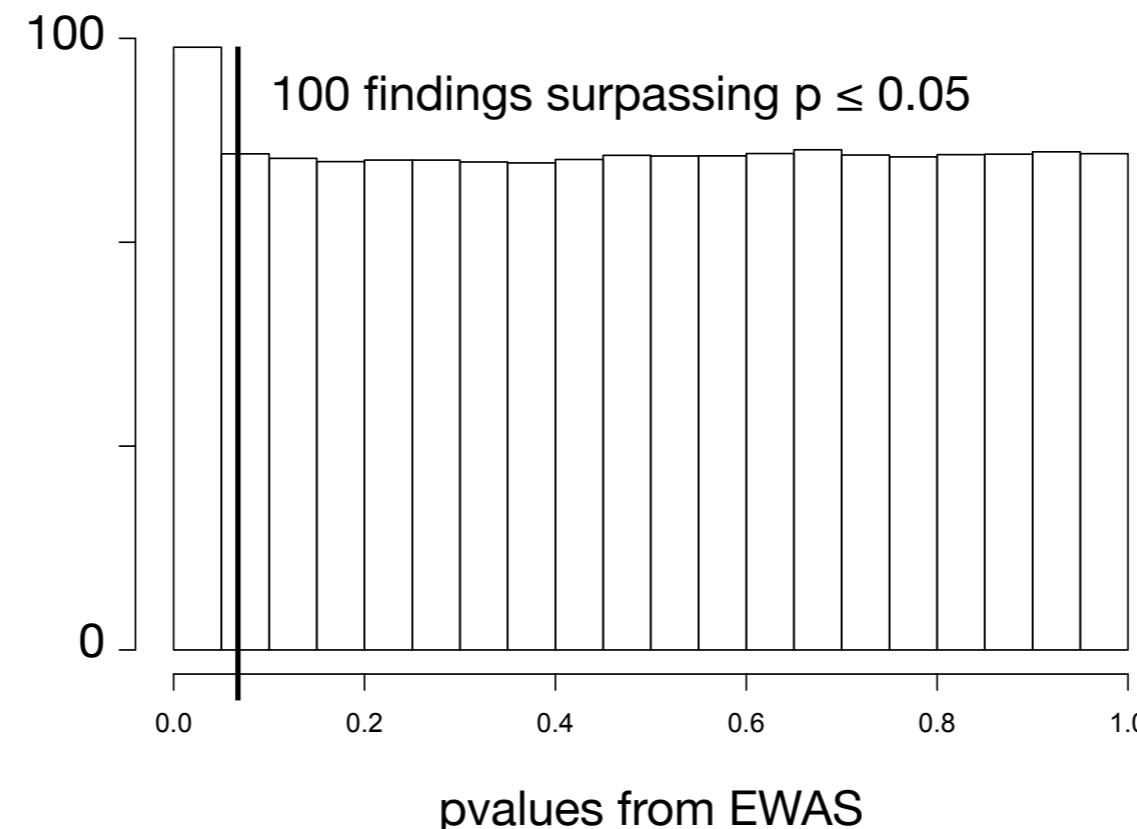


**False Discovery Rate Estimation:**  
The *expected* rate of false positives

$$= \frac{\# \text{ false positives} \leq \alpha}{\# \text{ findings} \leq \alpha}$$

$$\frac{50 \text{ false positives} \leq 0.05}{100 \text{ findings} \leq 0.05} = 0.5$$

? # false positives ( $\alpha$ )



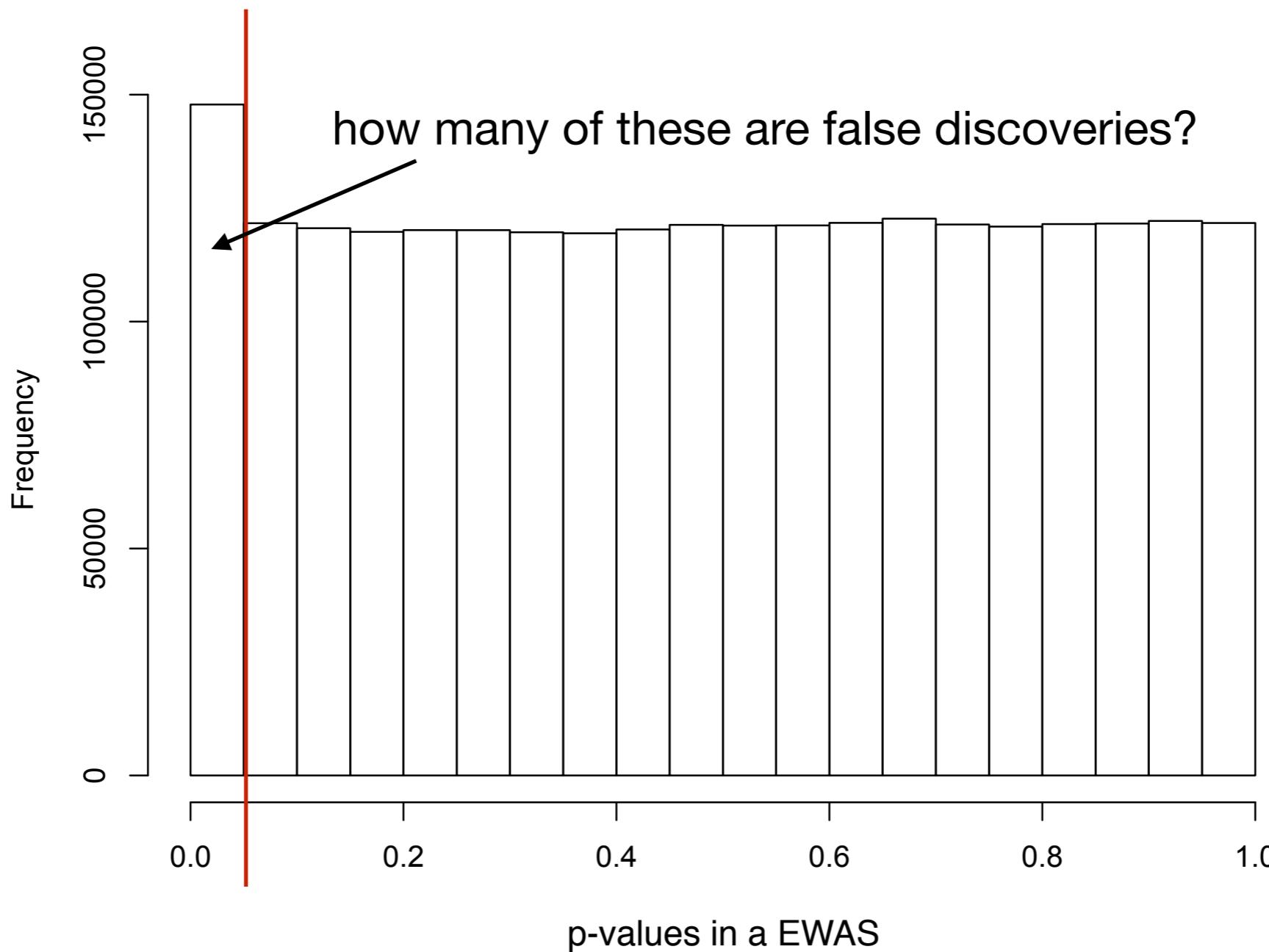
**TABLE 1**  
*Number of errors committed when testing  $m$  null hypotheses*

|                          | <i>Declared<br/>non-significant</i> | <i>Declared<br/>significant</i> | <i>Total</i> |
|--------------------------|-------------------------------------|---------------------------------|--------------|
| True null hypotheses     | $U$                                 | $V$                             | $m_0$        |
| Non-true null hypotheses | $T$                                 | $S$                             | $m - m_0$    |
|                          | $m - R$                             | $R$                             | $m$          |

We don't know  $V!$

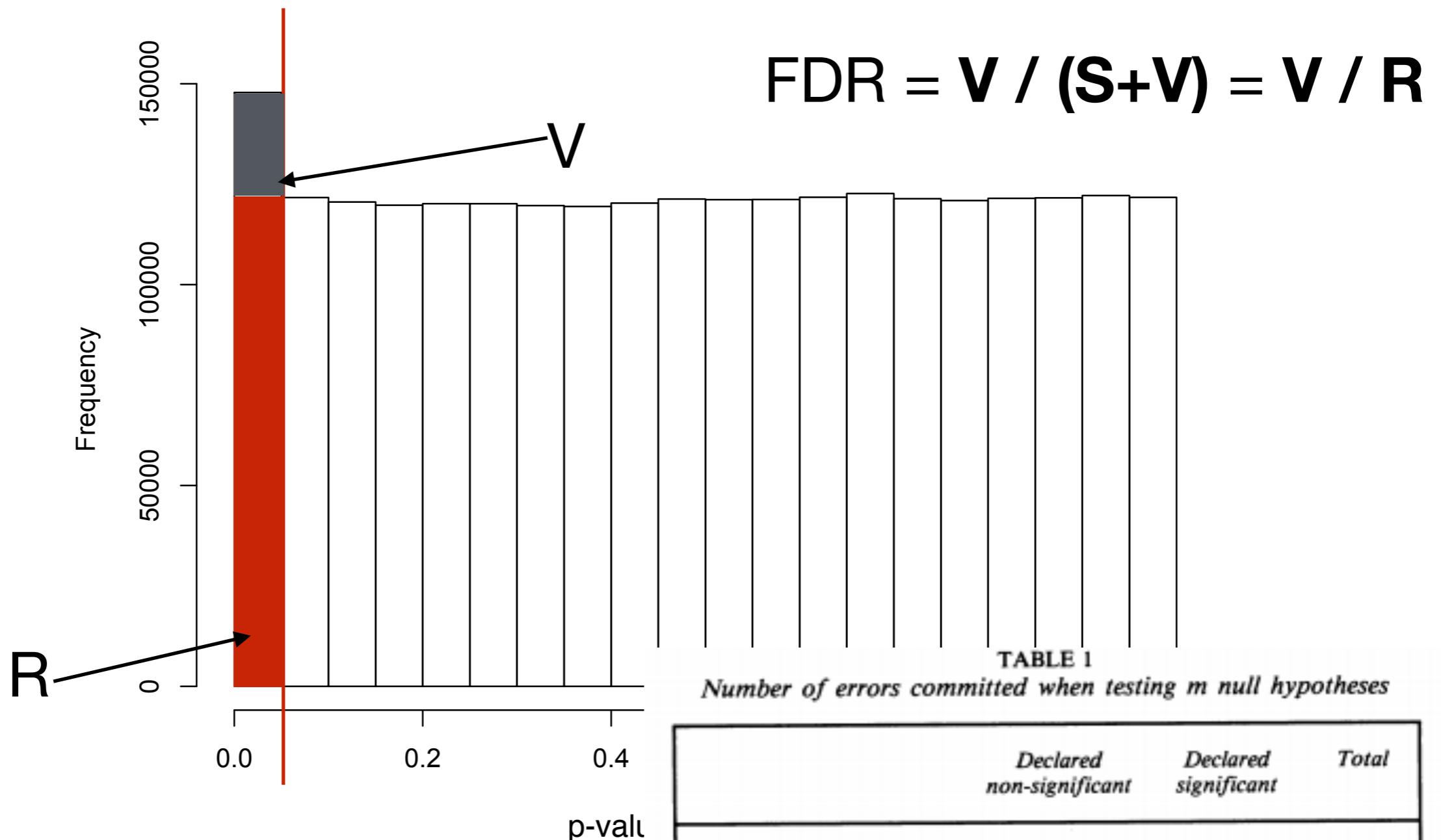
# What is the ***False Discovery Rate***?

*The expected number of false discoveries at a given significance threshold*



# What is the ***False Discovery Rate***?

*The expected number of false discoveries at a given significance threshold*



# How can I compute the ***False Discovery Rate?*** *empirically deriving the null distribution through permutation tests*

**False Discovery Rate Estimation:**  
The *expected* rate of false positives

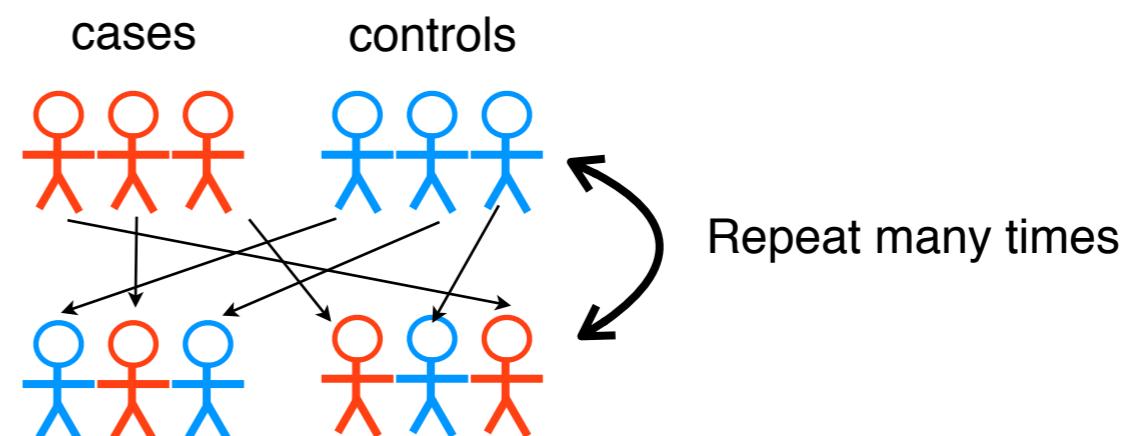
$$= \frac{\# \text{ false positives} \leq a}{\# \text{ findings} \leq a}$$

$$\frac{50 \text{ false positives} \leq 0.05}{100 \text{ findings} \leq 0.05} = 0.5$$

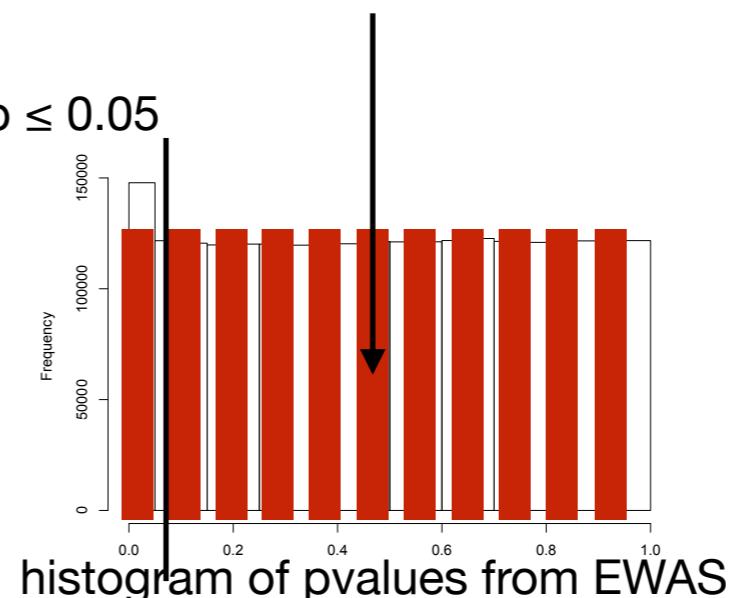
? # false positives (a)

“Shuffle” (permute) disease and non-diseased participants

Re-run EWAS



100 findings surpassing  $p \leq 0.05$



# How can I compute the *False Discovery Rate?*

## ***Benjamini-Hochberg “step-up” method***

first, choose a threshold,  $q$

Benjamini and Hochberg (1995) showed that when the test statistics are independent the following procedure controls the FDR at level  $q \cdot m_0/m \leq q$ .

Next, sort p-values

THE BENJAMINI HOCHBERG PROCEDURE. Let  $p_{(1)} \leq p_{(2)} \leq \dots \leq p_{(m)}$  be the ordered observed  $p$ -values. Define

$$(1) \quad \text{find } k \quad k = \max \left\{ i : p_{(i)} \leq \frac{i}{m} q \right\},$$

and reject  $H_{(1)}^0 \dots H_{(k)}^0$ . If no such  $i$  exists, reject no hypothesis.

$$p(i) * m/i \leq q$$

Benjamini and Hochberg (1995) showed that when the test statistics are independent the following procedure controls the FDR at level  $q \cdot m_0/m \leq q$ .

THE BENJAMINI HOCHBERG PROCEDURE. Let  $p_{(1)} \leq p_{(2)} \leq \dots \leq p_{(m)}$  be the ordered observed  $p$ -values. Define

$$(1) \quad k = \max \left\{ i : p_{(i)} \leq \frac{i}{m} q \right\},$$

and reject  $H_{(1)}^0 \dots H_{(k)}^0$ . If no such  $i$  exists, reject no hypothesis.

$$p(i) * m/i \leq q$$

0.01, 0.2, 0.5, 0.45, 0.06, 0.04, 0.004, 0.02, 0.1, 0.07

0.5, 0.45, 0.2, 0.1, 0.07, 0.06, 0.04, 0.02, 0.01, 0.004

$$0.004 * 10 / 1 \leq 0.05?$$

$$0.01 * 10 / 2 \leq 0.05?$$

$$0.02 * 10 / 3 \leq 0.05?$$

Any reach significance at an FDR < 0.05?

How can I compute the *False Discovery Rate?*  
*Benjamini-Hochberg “step-up” method*

0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04, 0.04

Any here reach significance at an FDR < 0.05?

How can I compute the *False Discovery Rate*?  
***Benjamini-Hochberg “step-up” method***

```
p.adjust(p, 'fdr')
```

What does this return?



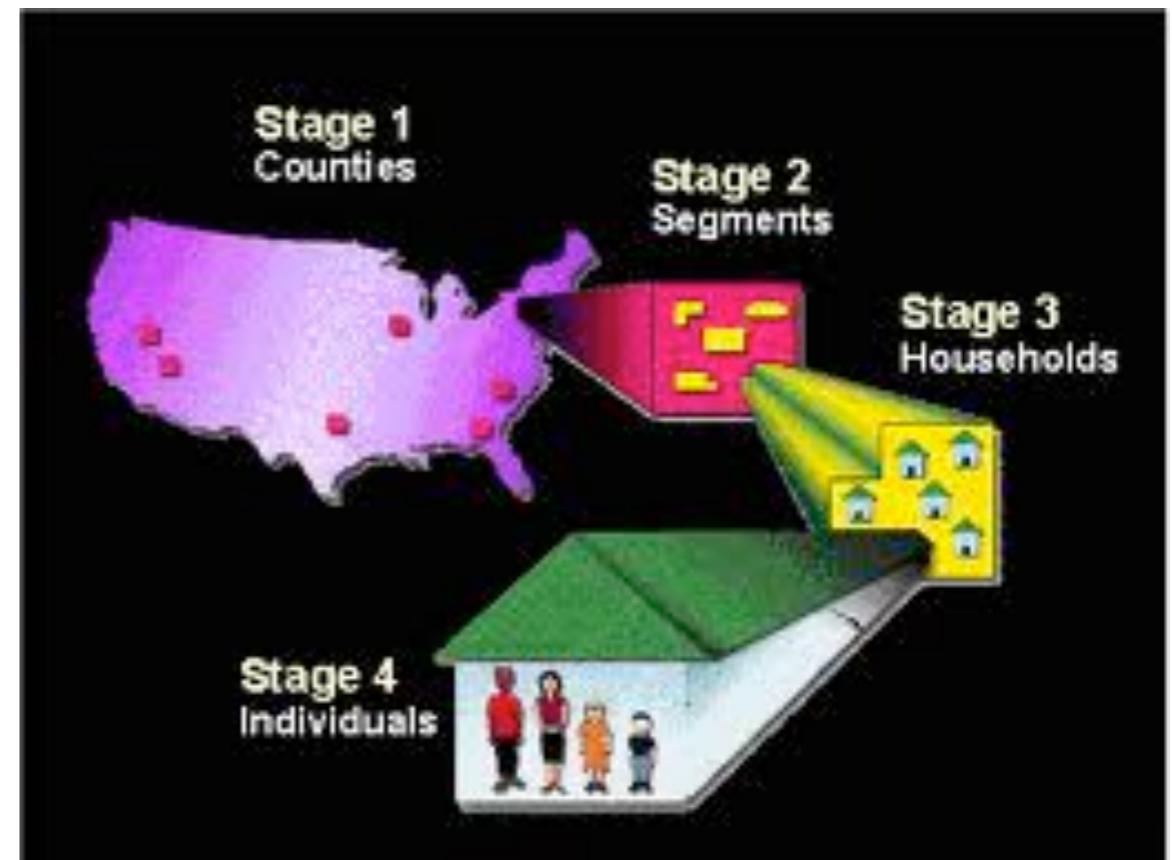
# Fully merged dataset: National Health and Nutrition Examination Survey

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

>250 exposures (serum + urine)

>200 quantitative clinical traits  
(e.g., serum glucose, lipids, body mass index, telomeres)

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 XWAS-related manuscripts

*preterm birth*

*type 2 diabetes*

*type 2 diabetes genetics*

*lipids*

*blood pressure*

*income*

*mortality*

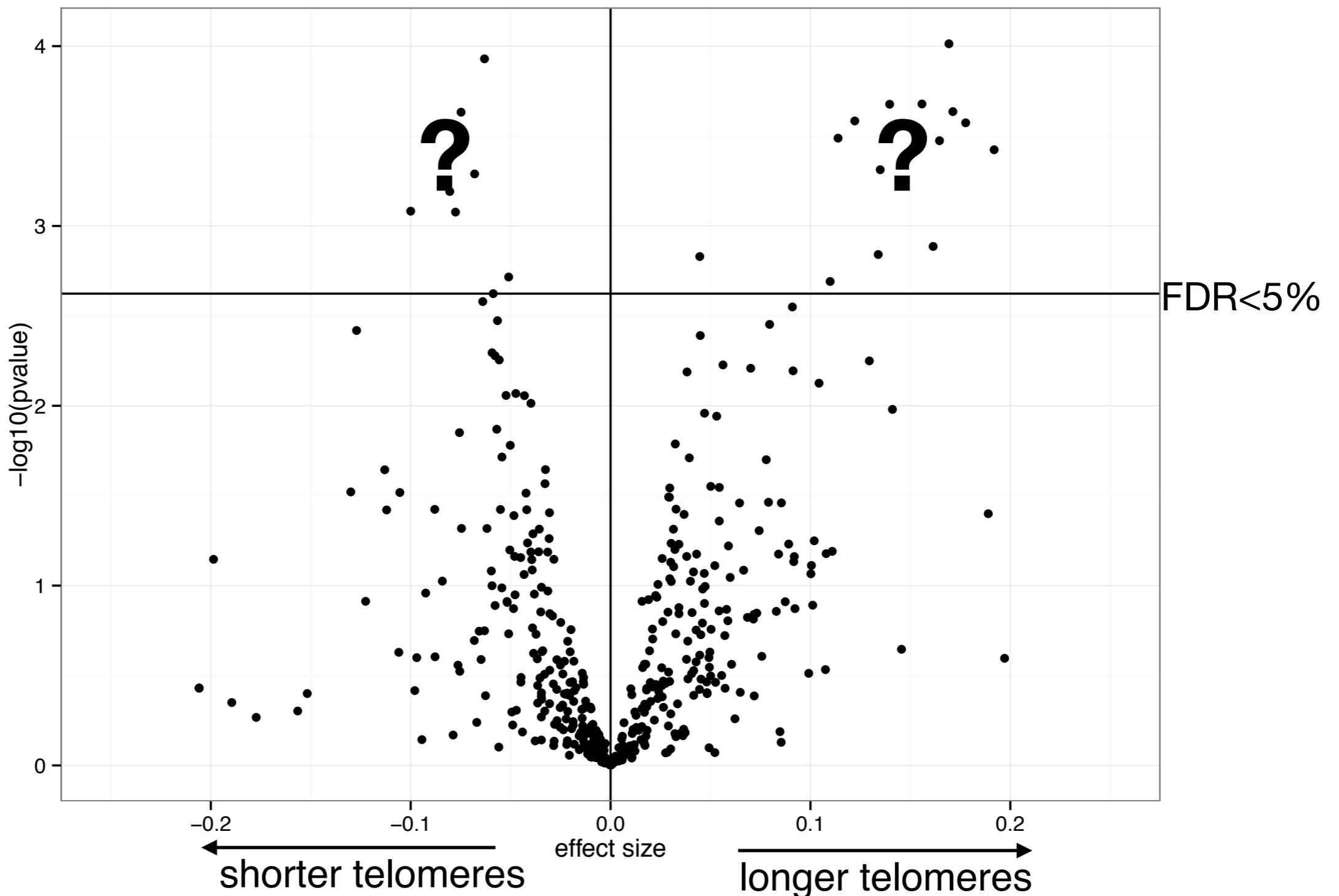
***telomere length***

methodology (5)

<http://correct>

# Associations in *Telomere Length*:

## Can you identify the associations in this graph?



median N=3000; N range: 300-7000

IJE, 2016

# Resources Index (for today's session)

**<http://bit.ly/xwas> with nhanes**

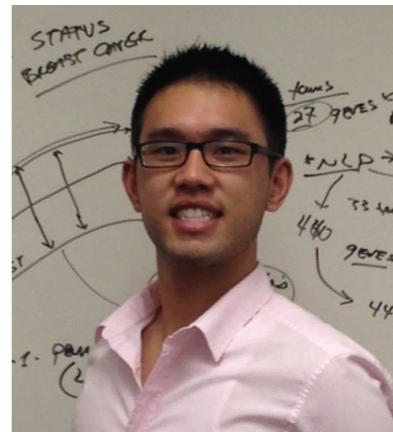
Please let us know if you are using the resources  
(or provide feedback)!

**Chirag**



  @chiragjp

**Nam**



  @nampho2

# Resources Index

## Papers and repositories

### **Papers:**

<https://paperpile.com/shared/PtvEae>

### **Sample size for EWAS:**

[https://github.com/jakemkc/ewas\\_sample\\_size](https://github.com/jakemkc/ewas_sample_size)

### **Correlation Globes (stratified):**

[https://github.com/jakemkc/exposome\\_variability](https://github.com/jakemkc/exposome_variability)

### **Correlation Globes:**

[https://github.com/chiragjp/exposome\\_correlation](https://github.com/chiragjp/exposome_correlation)

### **Exposome cohort data (NHANES 1999-2006)**

[https://github.com/chiragjp/nhanes\\_scidata](https://github.com/chiragjp/nhanes_scidata)

# Acknowledgements

## RagGroup

**Nam Pho**

**Chirag Lakhani**

**Adam Brown**

**Danielle Rasooly**

**Arjun Manrai**

Grace Mahoney

Matthew Roy

## Harvard DBMI

Isaac Kohane

Susanne Churchill

Stan Shaw

Jenn Grandfield

Michal Preminger

## Stanford

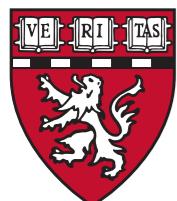
John PA Ioannidis



NIH Common Fund  
***Big Data to Knowledge***



**Agilent Technologies**



**HARVARD**  
**MEDICAL SCHOOL**

DEPARTMENT OF  
Biomedical Informatics

Chirag J Patel  
[chirag@hms.harvard.edu](mailto:chirag@hms.harvard.edu)  
[@chiragjp](https://twitter.com/chiragjp)  
[www.chiragjgroup.org](http://www.chiragjgroup.org)

