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Exposome: Challenges and Opportunities in the study of NCDs

Paul Elliott

Imperial College London
School of Public Health

Disclosures (Paul Elliott)

Dr Elliott ***receives funding*** from the UK Medical Research Council (MRC), National Institute for Health Research (NIHR), Public Health England (PHE), Department of Health, Home Office, Wellcome Trust, Academy of Medical Sciences, US National Institutes of Health (NIH), European Union. He ***chairs*** the Population & Systems Medicine Board at the MRC.

Of particular relevance to this presentation, he is *inter alia*

- Director of the *MRC – PHE Centre for Environment & Health*
- Principal Investigator (PI) of *UK MED–BIO* (Bioinformatics) funded by MRC
- Co-PI *MRC-NIHR National Phenome Centre* (Metabolomics)
- PI of the *Airwave study* funded by Home Office and NIHR
- Joint PI *INTERMAP Metabolomics Study* funded by NIH
- Co-PI *Metabolomics signatures of coronary artery disease (CAD) associated genotypes* funded by NIH

Outline

- Epidemiologic context
- Exposome
  - Metabolome
  - Nutriome
  - Genome (causal pathways)
- Cohorts
- Key takeaways

Epidemiological context

nature Vol 450|22 November 2007

FEATURE

Grand challenges in chronic non-communicable diseases

The top 20 policy and research priorities for conditions such as diabetes, stroke and heart disease.

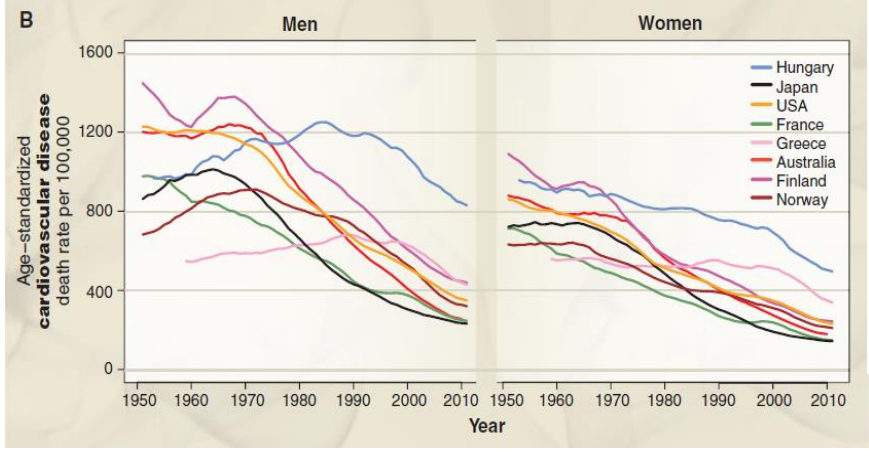
Abdallah S. Daar[1], Peter A. Singer[1], Deepa Leah Persad[1], Stig K. Pramming[2], David R. Matthews[3], Robert Beaglehole[4], Alan Bernstein[5], Leszek K. Borysiewicz[6], Stephen Colagiuri[7], Nirmal Ganguly[8], Roger I. Glass[9], Diane T. Finegood[10], Jeffrey Koplan[11], Elizabeth G. Nabel[12], George Sarna[1], Nizal Sarrafzadegan[13], Richard Smith[14], Derek Yach[15] and John Bell[16]

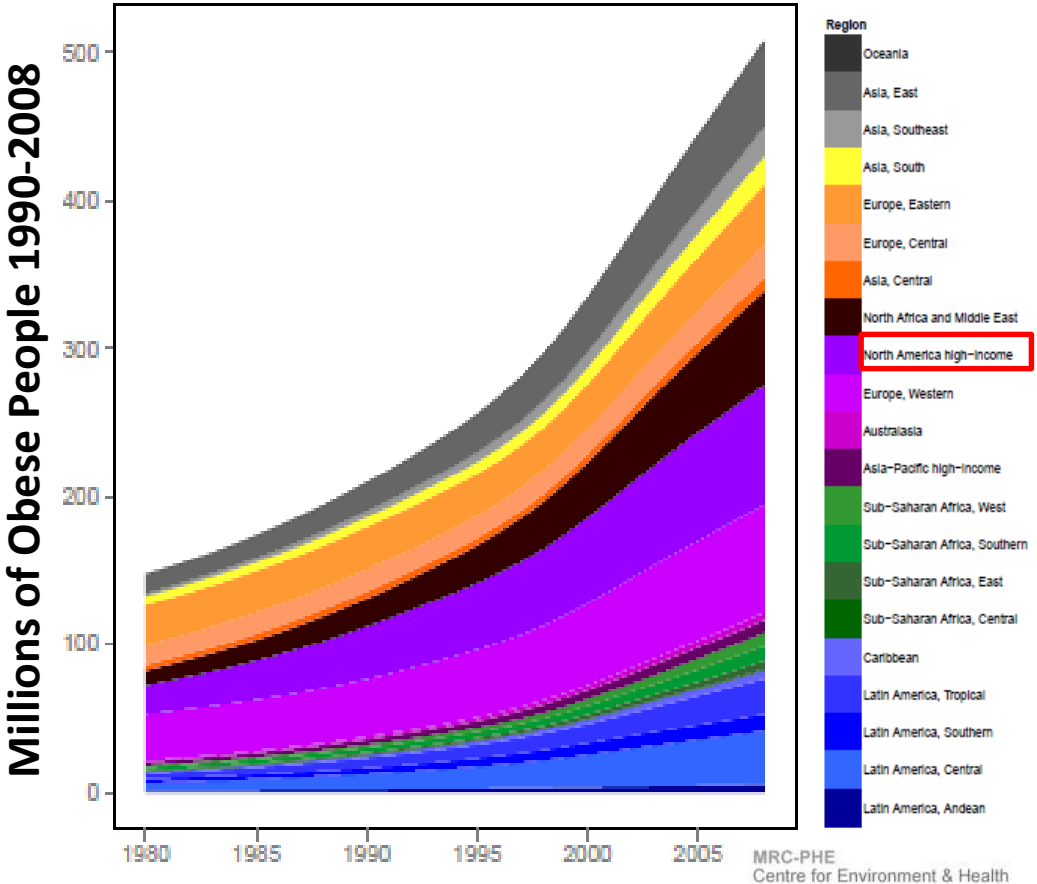
Chronic non-communicable diseases (CNCDs) are reaching epidemic proportions worldwide[1–3]. These diseases — which include cardiovascular conditions (mainly heart disease and stroke), some cancers, chronic respiratory conditions and type 2 diabetes — affect people of all ages, nationalities and classes.

The conditions cause the greatest global share of death and disability, accounting for around 60% of all deaths worldwide. Some 80% of chronic-disease deaths occur in low- and middle-income countries. They account for 44% of premature deaths worldwide. The number of deaths from these diseases is double the number of deaths that result from

Poor diet and smoking are two factors that contribute to the millions of preventable deaths that occur each year.

with known behavioural and pharmaceutical ... meet the challenges, and brings new talent





Ezzati M & Riboli E New Engl J Med 2013

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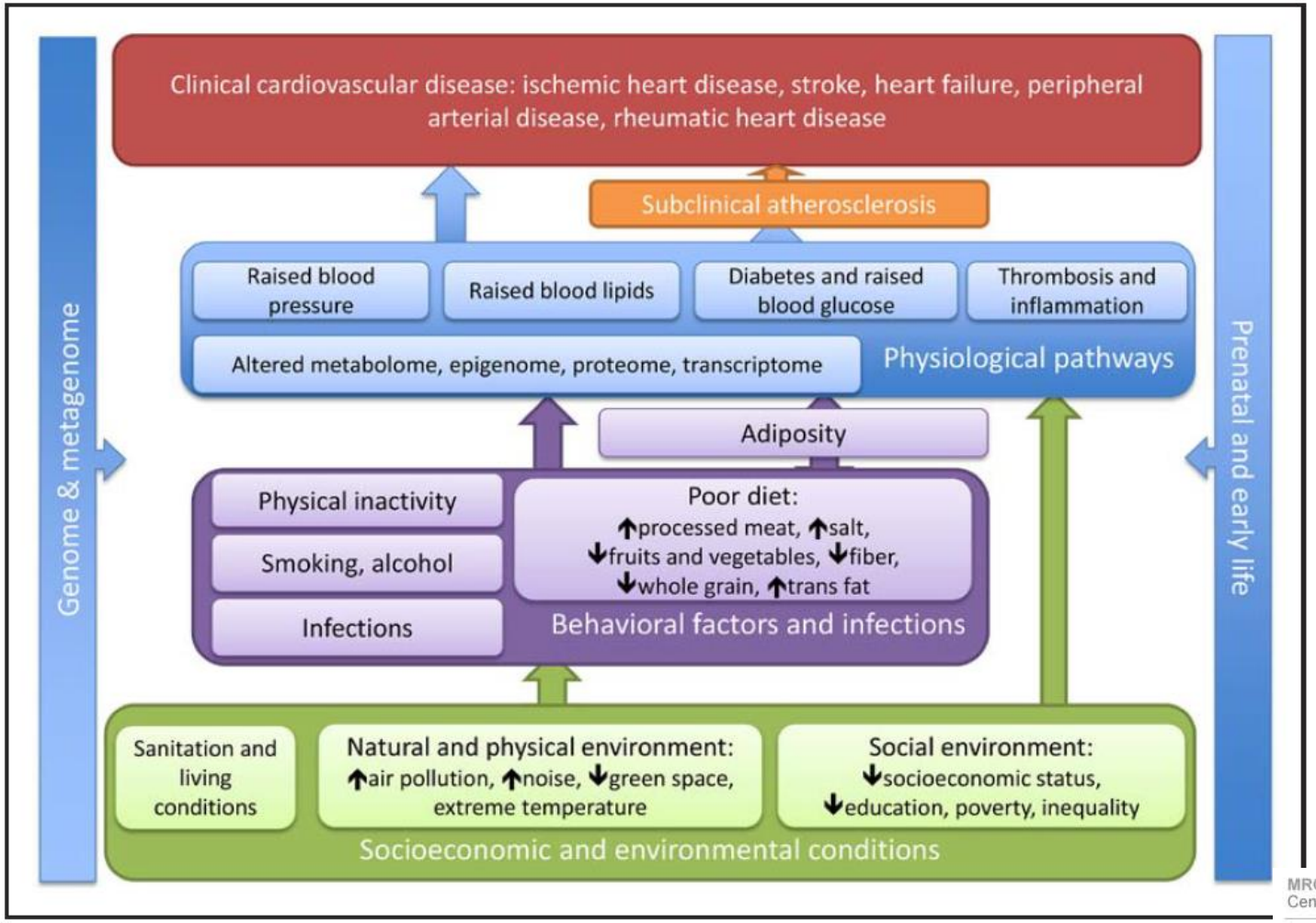
Upstream and proximal determinants of cardiovascular disease



Tzoulaki et al. *Circulation* 2016; 133:2314-33

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Molecular Systems Biology 3; Article number 124; doi:10.1038/msb4100163
Citation: *Molecular Systems Biology* 3:124

www.molecularsystemsbiology.com

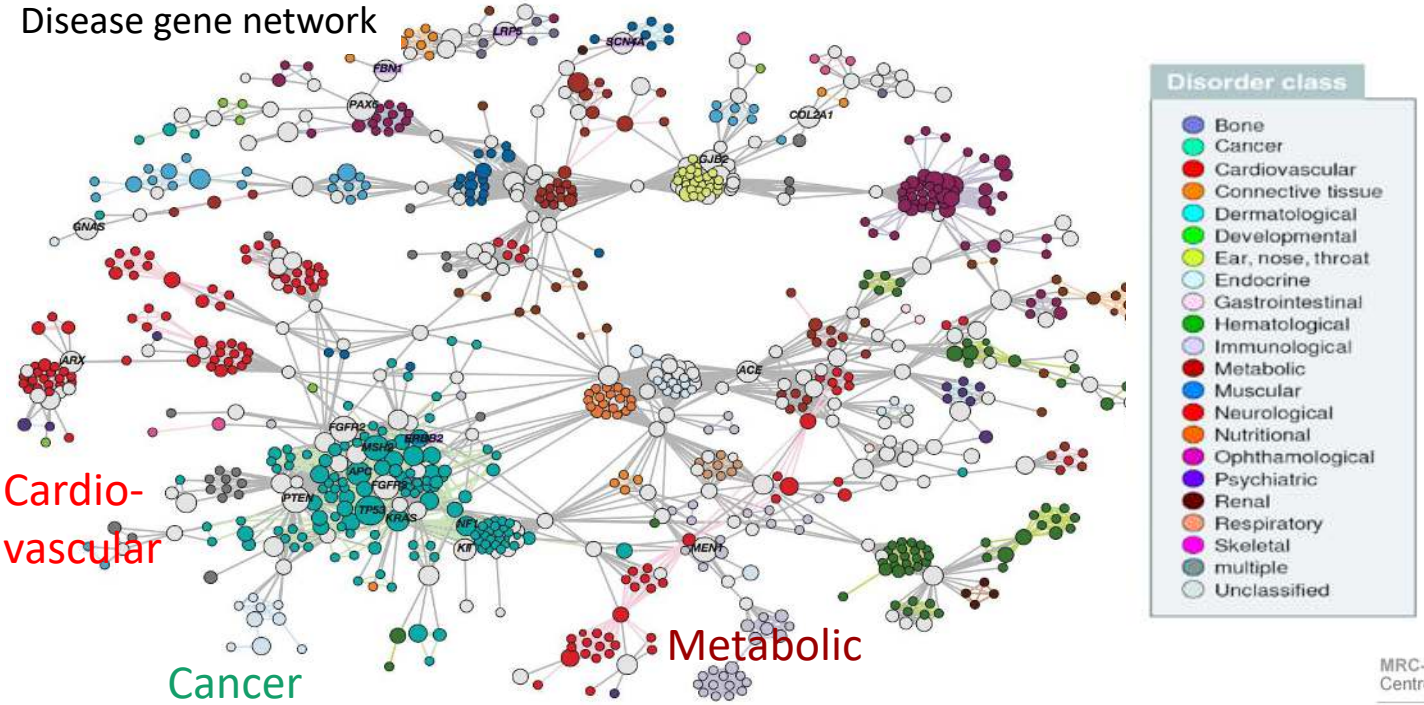
PERSPECTIVE

Barabasi et al (2007)

molecular systems biology

Human disease classification in the postgenomic era: A complex systems approach to human pathobiology

Disease gene network



Cardio-vascular

Cancer

Metabolic

Most human diseases are connected at some genetic level

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Molecular Systems Biology 3; Article number 124; doi:10.1038/msb4100163
Citation: *Molecular Systems Biology* 3:124

www.molecularsystemsbiology.com

Barabasi et al (2007)

molecular systems biology

PERSPECTIVE

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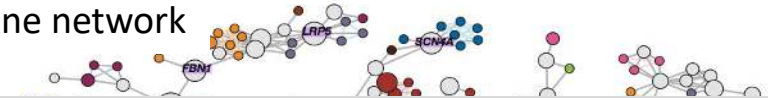
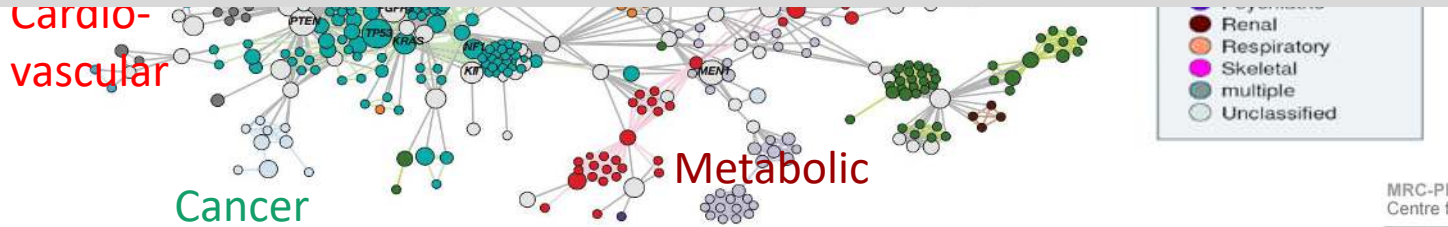


"Genetics loads the gun, but Environment pulls the trigger"

After Elliott Proctor Joslin MD, Br Med J 1991; 302: 1231



Most human diseases are connected at some genetic level

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Challenge

While ***genetic data*** are a (fixed) digital read-out...

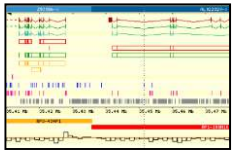
Environmental/lifestyle ***exposure data*** vary over the lifecourse, are continuously distributed, with wide dynamic range...

…and ***difficult to measure***

New approaches required to capture effects of environmental exposures on NCD risk!

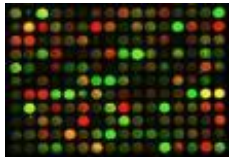
Exposome

OMICS

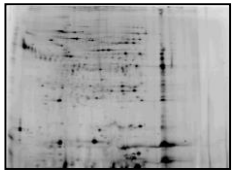


Genome

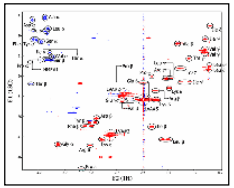
Epigenome



Transcriptome

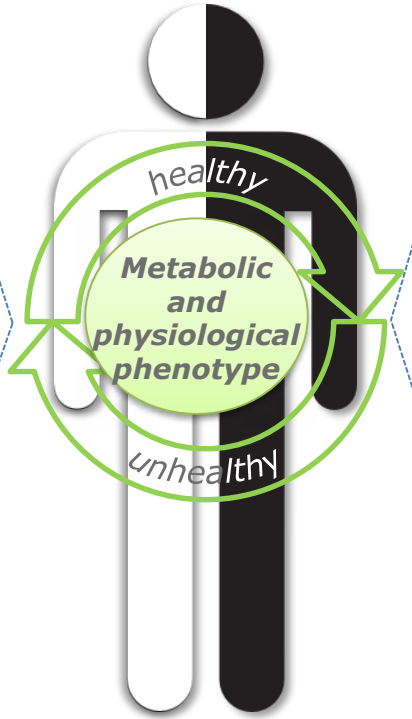


Proteome



Metabolome

Systems approach



ENVIRONMENT

After Rappaport & Smith *Science* 2010; 330:460-1

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Concept

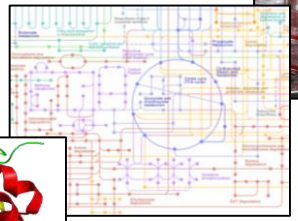
Exposure

Clinical phenotype

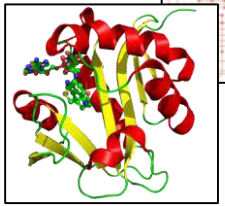
Molecular phenotype

Biomarkers

Systems



Pathways



Molecular

Linkage and Integration

Health

Policy & Action

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Metabolome…

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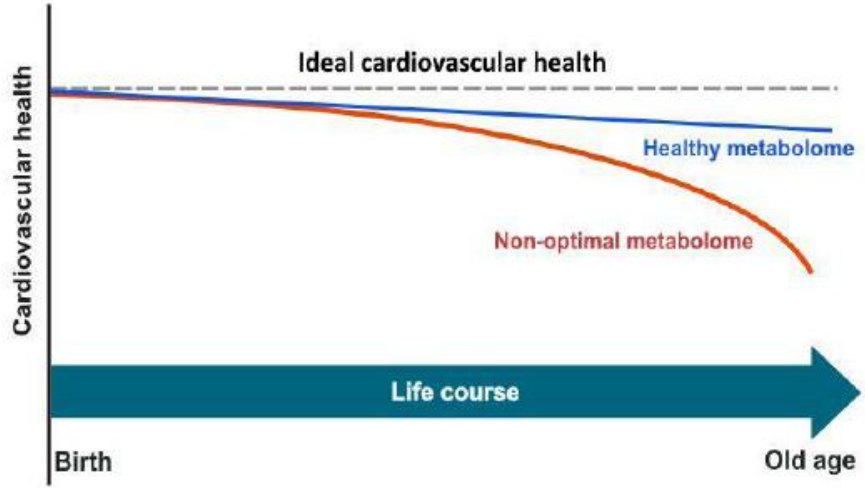
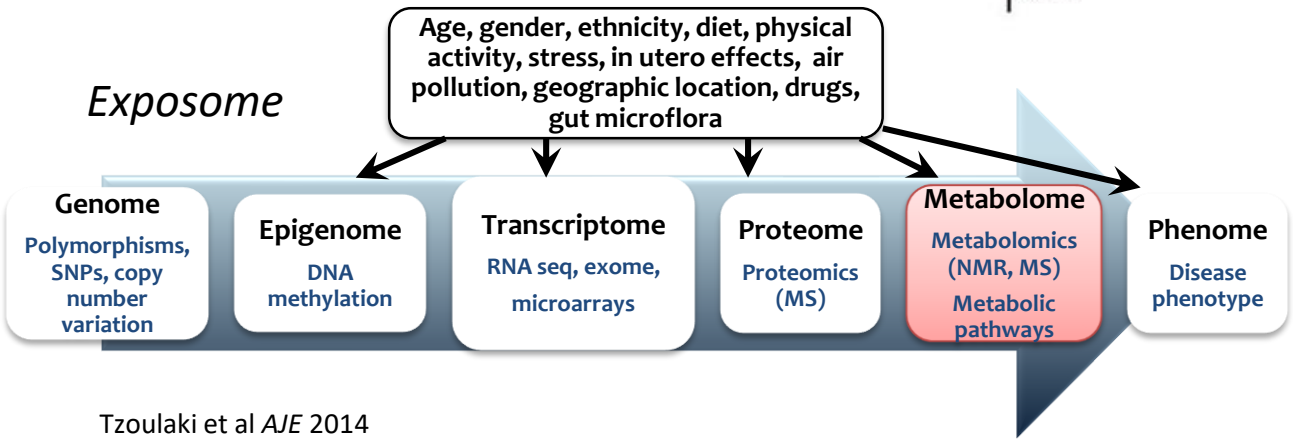
Metabolomics

- Measurement of small molecules in biological samples (e.g. blood, urine)
- Metabolites represent downstream biochemical end products that are close to the phenotype
- Link between environmental stressors, intrinsic metabolism, genetic information, health and disease





Tzoulaki et al *AJE* 2014

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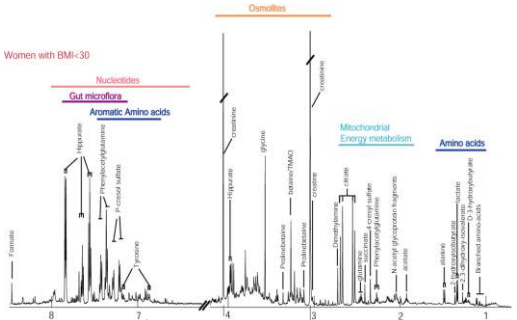
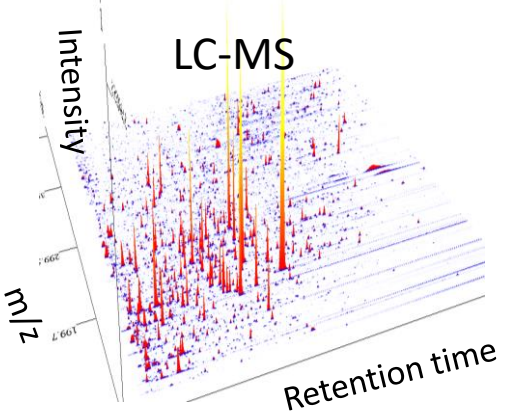
Metabolic Profiling

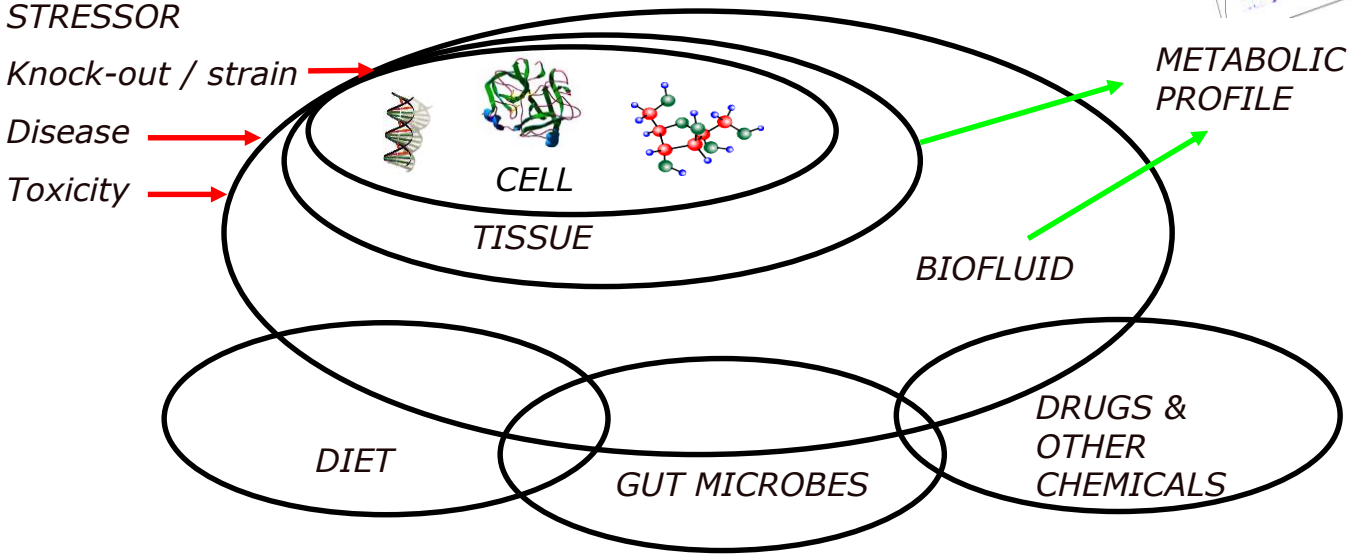
NMR



Urinary NMR spectrum



LC-MS



System ⟷ Environment

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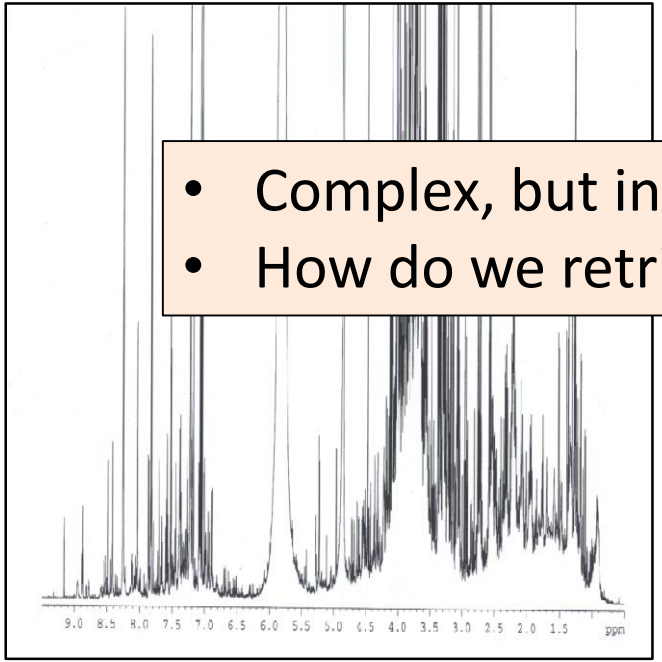
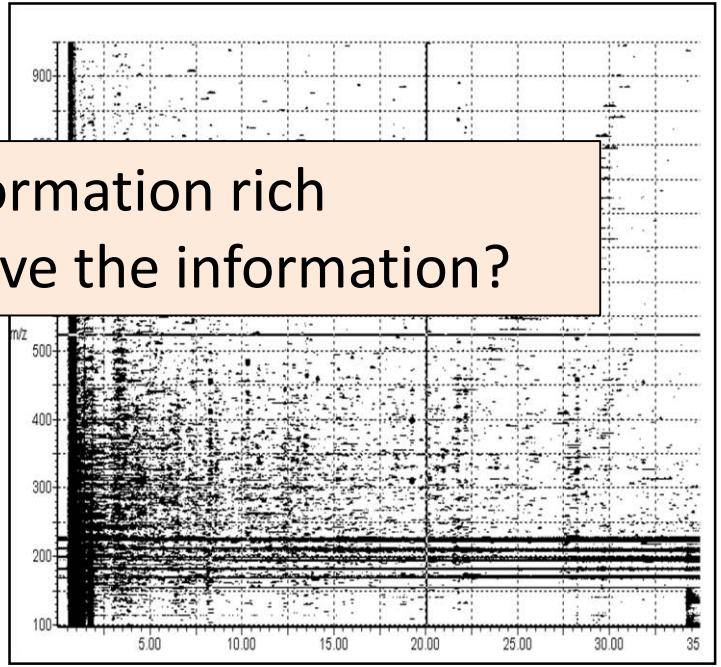
The Challenge of Metabolomic Data

NMR



~1000s signals,100s metabolites

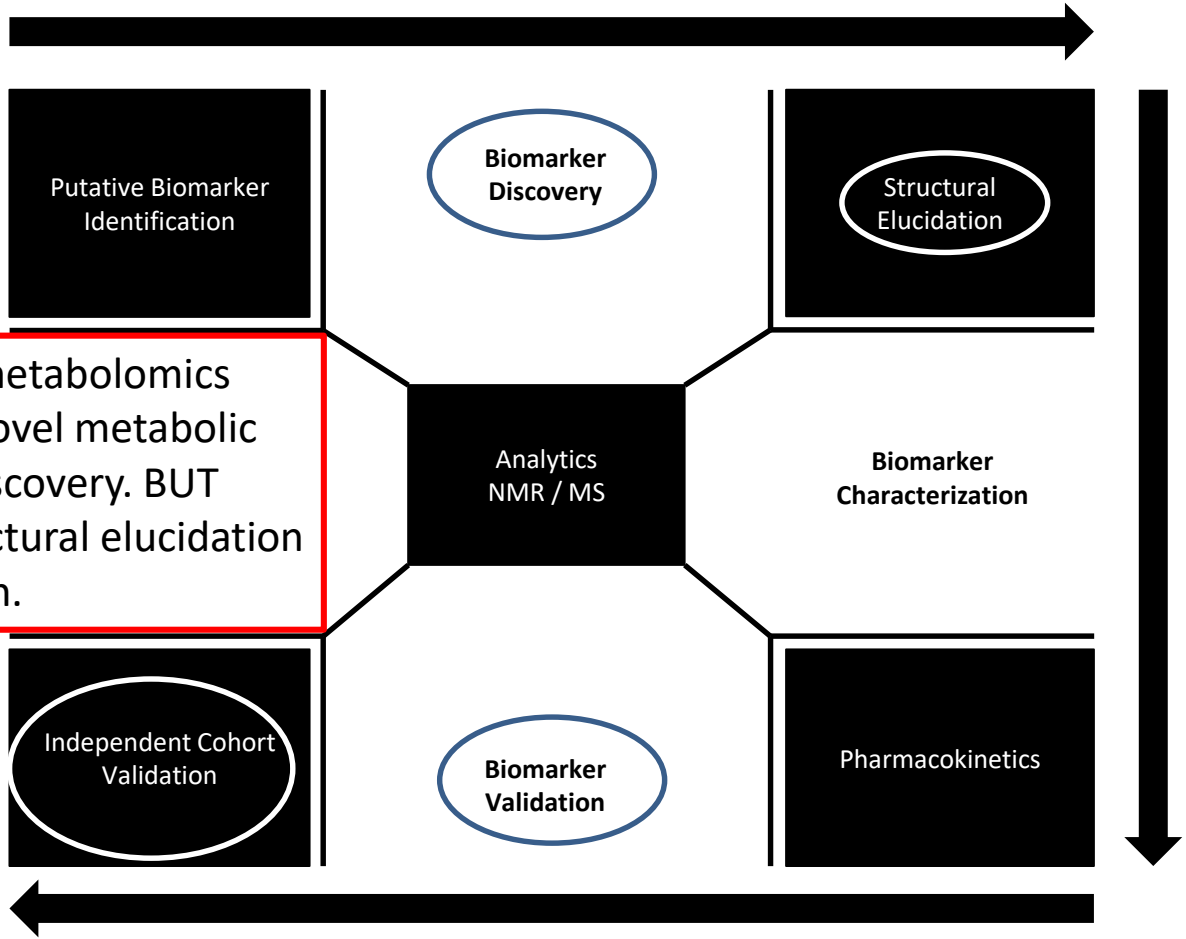
LC-MS



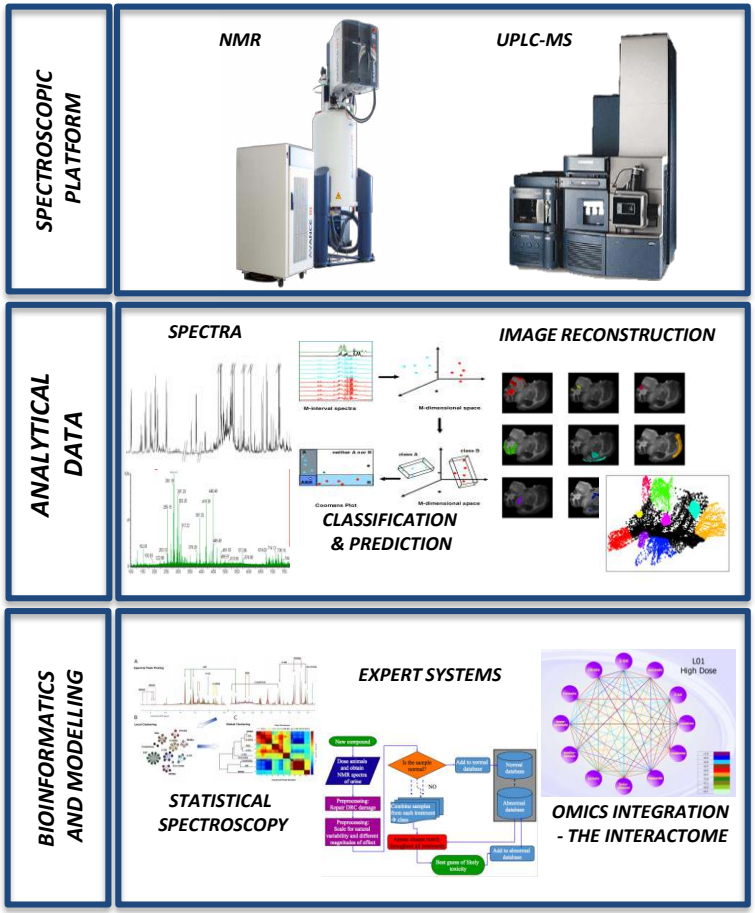
~10,000s signals,1000s (?) metabolites

- Complex, but information rich
- How do we retrieve the information?

Measuring The Metabolome



Untargeted metabolomics can lead to novel metabolic biomarker discovery. BUT requires structural elucidation and validation.



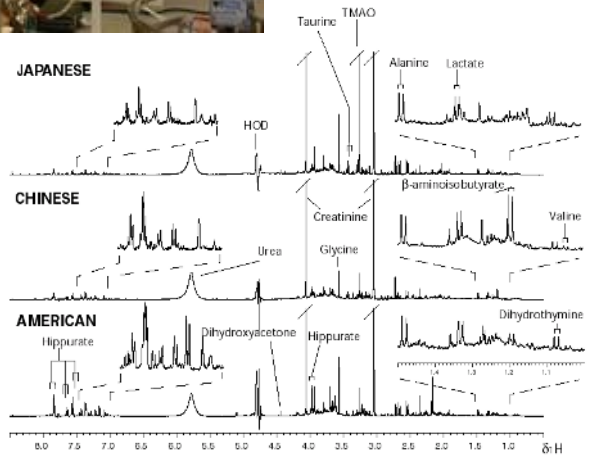
Steps in the analysis

- *State-of-the-art (mass spectrometric and NMR spectroscopic) analyses for metabolic finger-printing of biofluids*
- *Combine metabolic profiling with clinical, lifestyle and other –omics datasets*
- *Bioinformatic and pathway analyses*
- ***International phenome centres – common methods & standardization***

National Phenome Centre

MRC-NIHR National Phenome Centre

Metabolic phenotyping -^{1}H NMR analysis of 24-hr urine samples: INTERMAP Study (1996-9)



- 4,680 men & women ages 40-59
- 17 population samples, UK, USA, China, Japan
  - Eight BP measurements
  - Four 24-hr dietary recalls
  - Two 24-hr urine collections (3-6 weeks apart)

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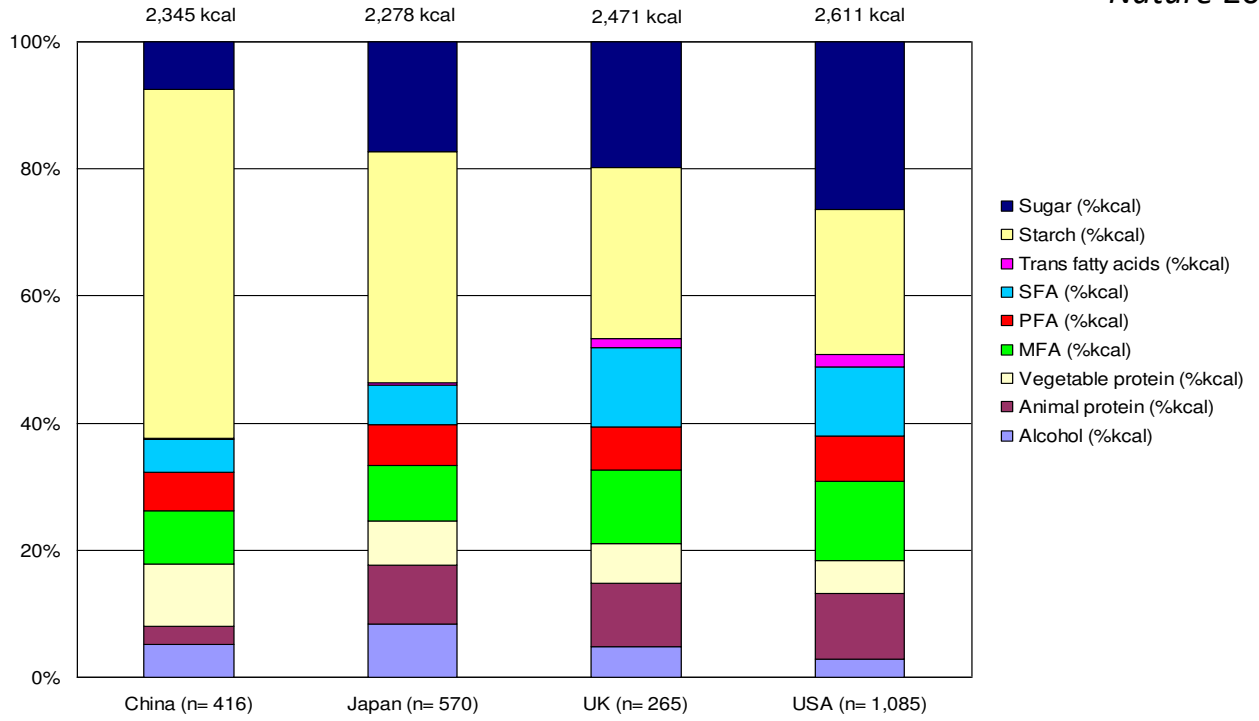
Human metabolic phenotype diversity and its association with diet and blood pressure

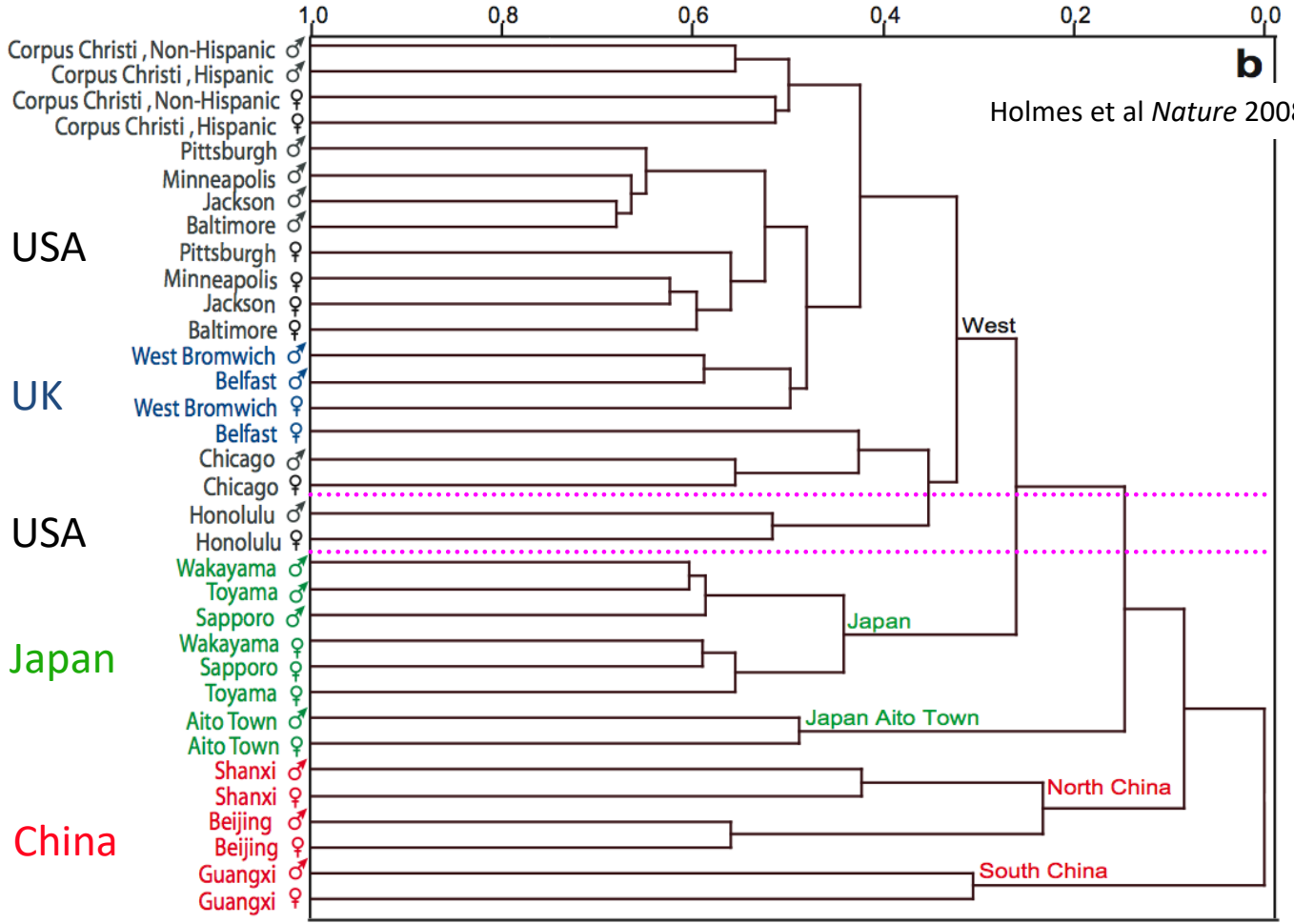
Elaine Holmes[1]*, Ruey Leng Loo[1,2]*, Jeremiah Stamler[3], Magda Bictash[1,2], Ivan K. S. Yap[1,2], Queenie Chan[2], Tim Ebbels[1], Maria De Iorio[2], Ian J. Brown[2], Kirill A. Veselkov[1], Martha L. Daviglus[3], Hugo Kesteloot[4], Hirotsugu Ueshima[5], Liancheng Zhao[6], Jeremy K. Nicholson[1] & Paul Elliott[2]

Nature 2008; 493:396-400



Population Metabolic Phenotype Mapping (INTERMAP)

China, Japan, UK, USA - 17 sub-populations, male/female, N = 4630 (24-h urine)



Holmes et al *Nature* 2008;493:396-400

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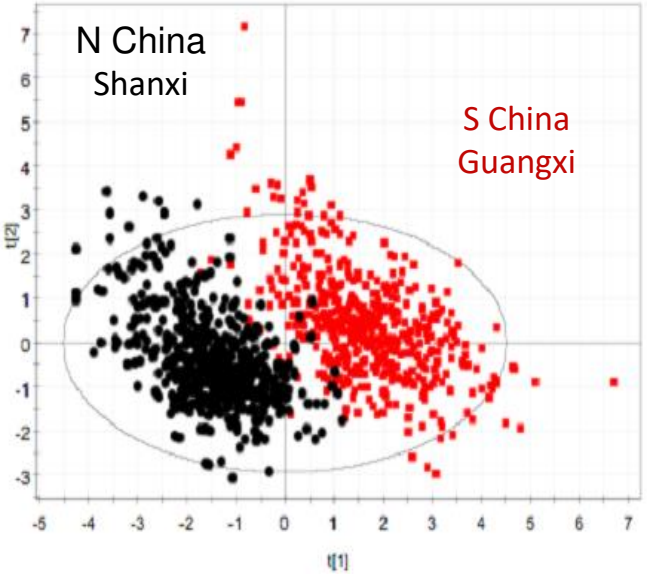
INTERMAP Study – Chinese samples



	Mean (SD)	
Trait	**N China (N=523)**	**S China (N=244)**
SBP mm Hg	123.8 (18.6)	115.4 (13.0)
Ur Na mmol/24h	271.4 (88.3)	139.2 (55.5)
Ur Na/K ratio	7.8 (2.4)	3.7 (1.5)
Ca mg/1000 kcal	136.5 (48.4)	175.0 (62.5)
Mg mg/1000 kcal	133.2 (38.7)	198.2 (27.2)

Yap et al. *J Proteome Res* 2010;9(12):6647-54

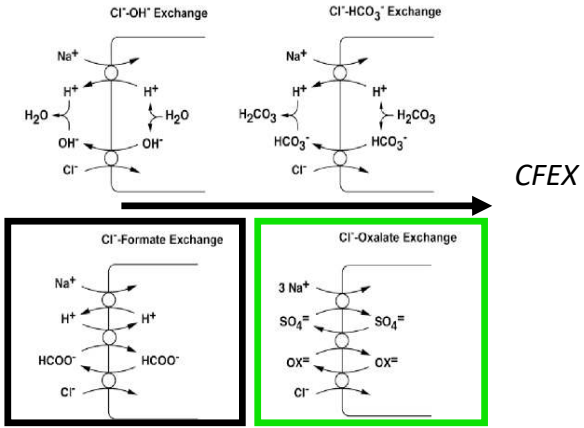
METABOLOME WIDE ASSOCIATION STUDIES: METABOLIC PHENOTYPE LINKAGE TO HUMAN BLOOD PRESURE

Table 1: Estimated mean differences* in systolic and diastolic BP (Z-scores‡)

Urinary metabolite	A				B			
	Adjusted for BMI†				Adjusted for BMI†			
	Systolic blood pressure							
Alanine	**2.69**	**(6.06)**	0.40	(0.92)	2.66	(5.54)	1.13	(2.43)
Formate	**-1.19**	**(-2.62)**	-1.42	(-3.29)	-1.94	(-3.92)	-1.04	(-2.20)
Hippurate	**-2.10**	**(-4.85)**	-1.63	(-3.95)	-1.72	(-3.70)	-0.82	(-1.83)
NMNA**	**-0.09**	**(-0.21)**	0.20	(0.49)	0.00	(0.00)	0.65	(1.53)

***N* methyl-nicotinate

"Metabolome-Wide Association Studies" for novel hypothesis generation… e.g…..a possible new role for formate in human BP regulation?



CFEX

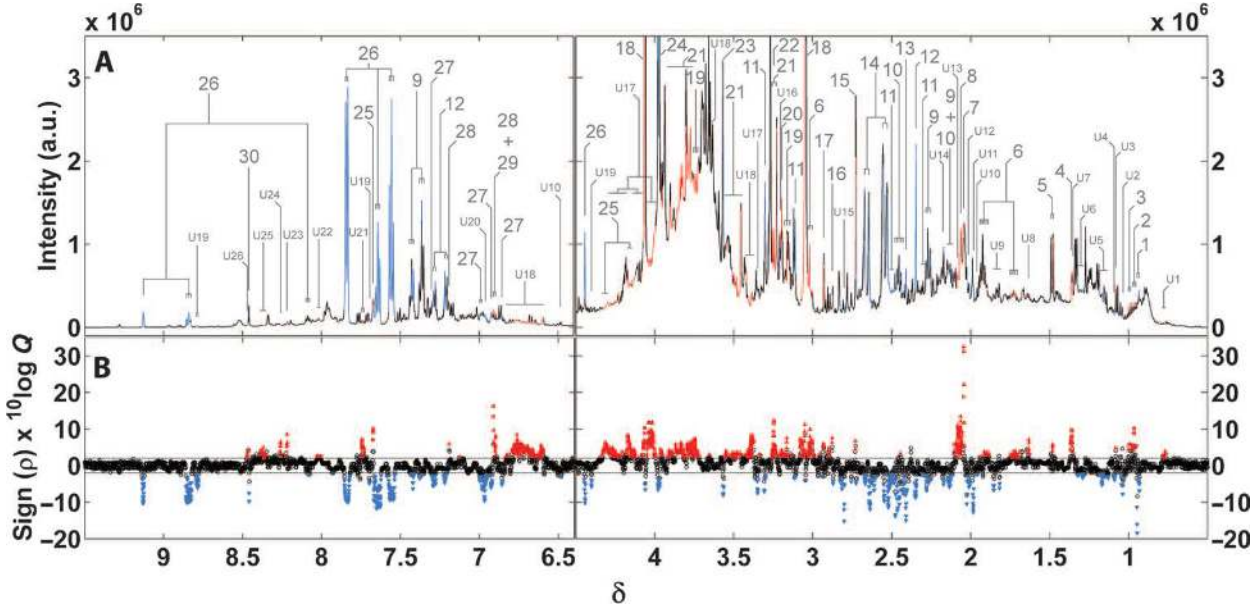
Holmes et al *Nature* 2008;493:396-400

METABOLOMICS

Urinary metabolic signatures of human adiposity

INTERMAP USA: N=1,880

Paul Elliott,[1*†] Joram M. Posma,[1,2†] Queenie Chan,[1] Isabel Garcia-Perez,[2] Anisha Wijeyesekera,[2] Magda Bictash,[2] Timothy M. D. Ebbels,[2] Hirotsugu Ueshima,[3] Liancheng Zhao,[4] Linda van Horn,[5] Martha Daviglus,[5,6] Jeremiah Stamler,[5] Elaine Holmes,[2] Jeremy K. Nicholson[2*]



1: ketoleucine, 2: leucine, 3: valine, 4: 2-hydroxyisobutyrate, 5: alanine, 6: lysine, 7: N-acetyl signals from urinary glycoproteins, 8: N-acetyl neuraminate, 9: phenylacetylglutamine, 10: glutamine, 11: proline betaine, 12: 4-cresyl sulfate,13: succinate, 14: citrate, 15: dimethylamine, 16: TMA, 17: dimethylglycine, 18: creatinine, 19: ethanolamine, 20: O-acetyl carnitine, 21: glucose, 22: 3-methylhistidine, 23: glycine, 24: hippurate, 25: pseudouridine, 26: NMNA, 27: 3-hydroxymandelate, 28: tyrosine, 29: 4-hydroxymandelate, 30: formate, U1 to U26 unidentified

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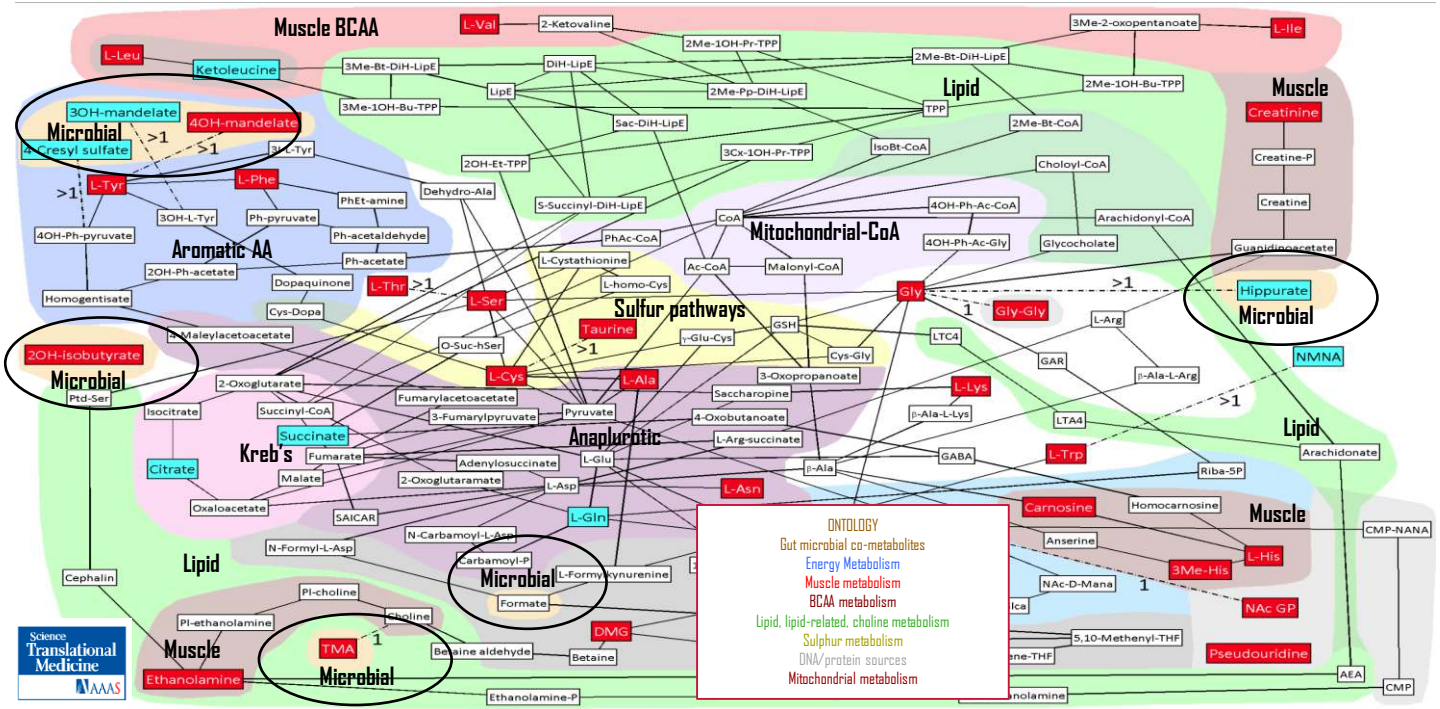
"METABONETWORKS": VISUALIZATION SYSTEM FOR BMI BIOMARKERS

Minimally-structured symbiotic metabolic network connecting BMI biomarkers, n=1880 US citizens



www.ScienceTranslationalMedicine.org 29 April 2015 Vol 7 Issue 285 285ra62

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Nutriome…

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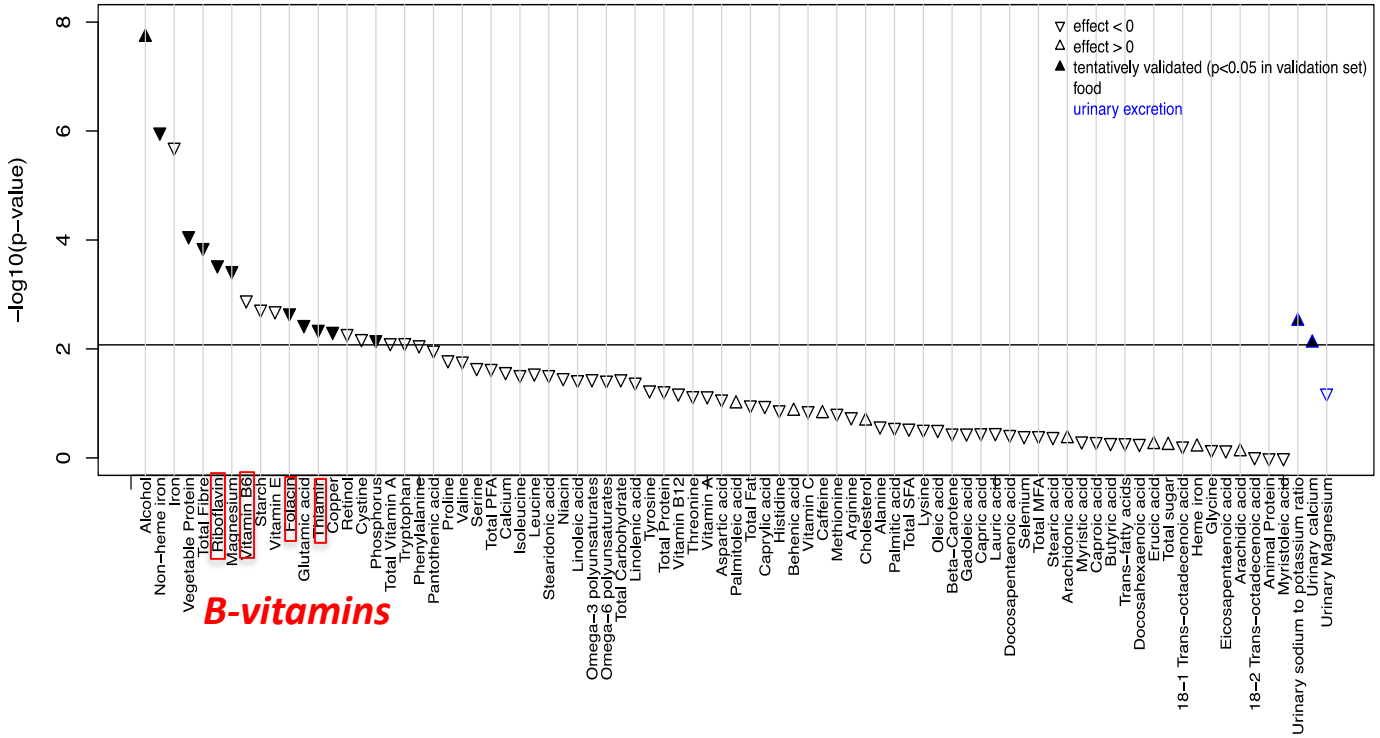
Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Nutrient-Wide Association Study on Blood Pressure

Ioanna Tzoulaki, PhD;* Chirag J. Patel, PhD;* Tomonori Okamura, MD, PhD; Queenie Chan, PhD; Ian J. Brown, PhD; Katsuyuki Miura, MD, PhD; Hirotsugu Ueshima, MD, PhD; Liancheng Zhao, MD; Linda Van Horn, PhD; Martha L. Daviglus, MD, PhD; Jeremiah Stamler, MD; Atul J. Butte, MD, PhD; John P.A. Ioannidis, MD, DSc; Paul Elliott, MB BS, PhD

INTERMAP Study



Tzoulaki et al. *Circulation 2012;126:2456-2464*

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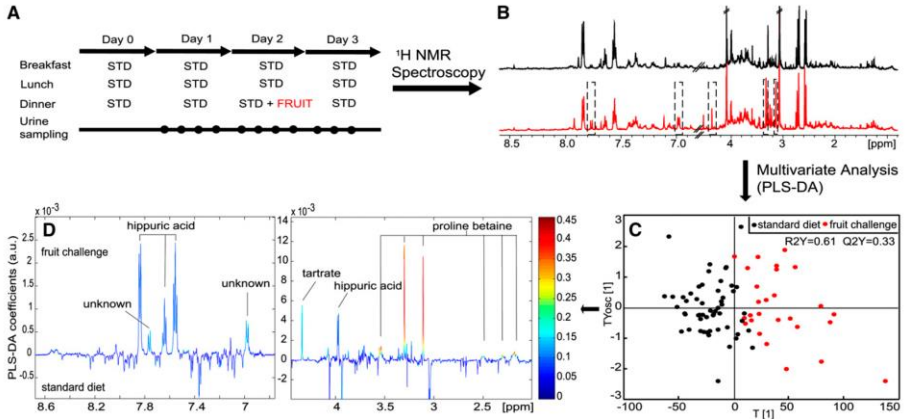
Dietary metabolome

Metabolic profiling strategy for discovery of nutritional biomarkers: proline betaine as a marker of citrus consumption[1–3]

Silke S Heinzmann, Ian J Brown, Queenie Chan, Magda Bictash, Marc-Emmanuel Dumas, Sunil Kochhar, Jeremiah Stamler, Elaine Holmes, Paul Elliott, and Jeremy K Nicholson



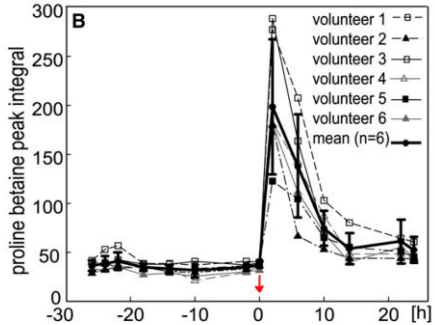


FIGURE 2. Urinary excretion kinetics of proline betaine after orange juice consumption (n = 6). A: Proline betaine singlet at δ 3.11 was integrated over the spectral region δ 3.106–3.116 as shown where the peak overlap is minimal. B: Mean and SD proline betaine integral (solid bold line) and the proline betaine integral for each of the 6 volunteers plotted over time. The red arrow indicates the time of orange juice consumption. ppm, parts per million.

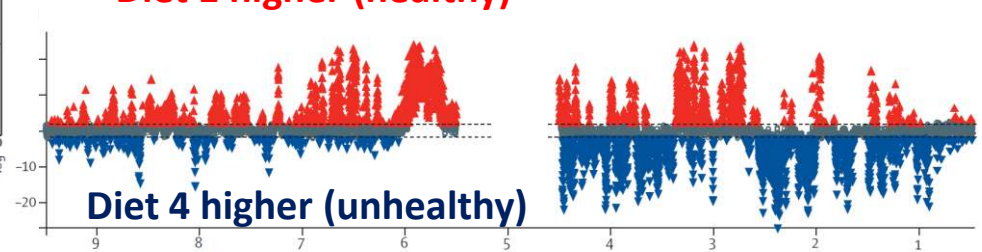
Am J Clin Nutr 2010;92:436–43

Objective assessment of dietary patterns by use of metabolic phenotyping: a randomised, controlled, crossover trial

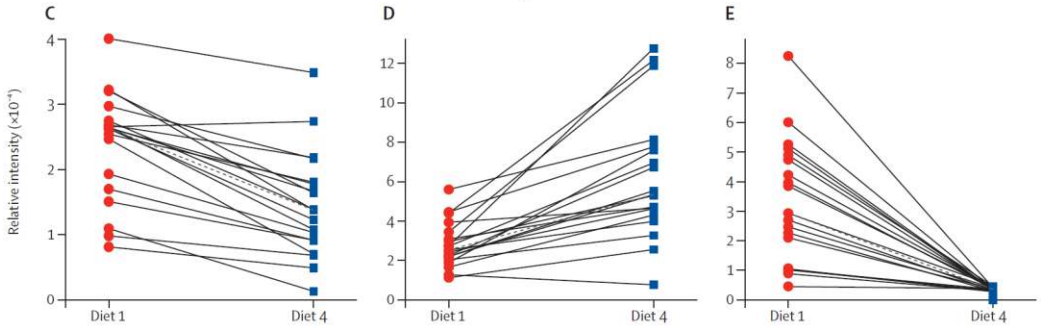
Isabel Garcia-Perez, Joram M Posma*, Rachel Gibson, Edward S Chambers, Tue H Hansen, Henrik Vestergaard, Torben Hansen, Manfred Beckmann, Oluf Pedersen, Paul Elliott, Jeremiah Stamler, Jeremy K Nicholson, John Draper, John C Mathers, Elaine Holmes*, Gary Frost**

Lancet Diabetes Endocrinol 2017; 5: 184–95

Diet 1 higher (healthy)



Diet 4 higher (unhealthy)



hippurate carnitine tartrate

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Cohorts…

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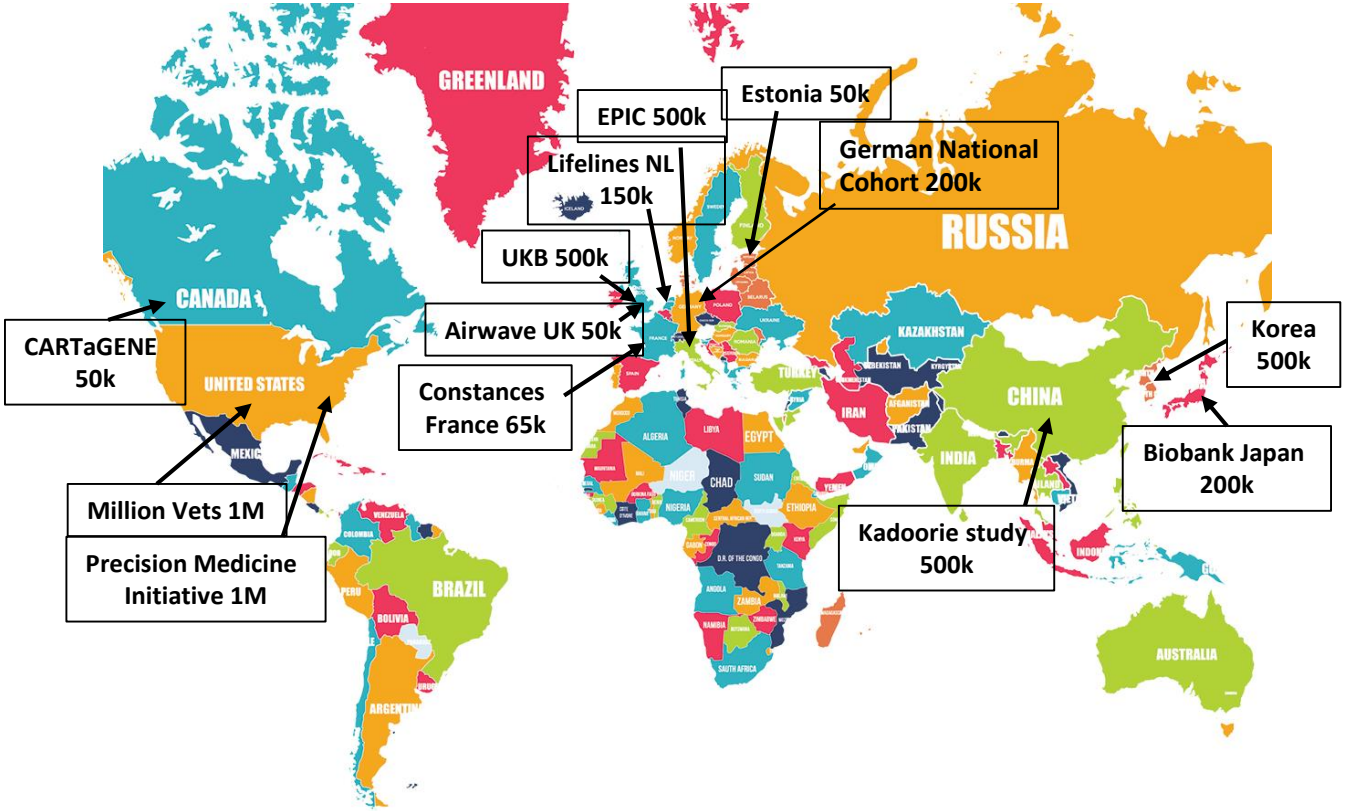
Large cohort studies (examples)



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Public Health England | MRC | Imperial College London | King's College London

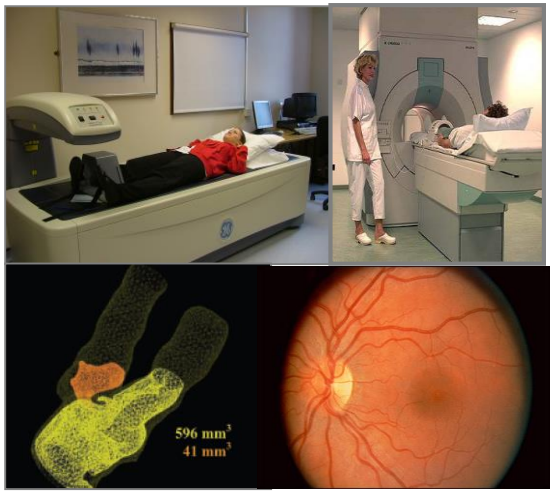
UK Biobank

- Clinical & lifestyle data and stored samples on 500k men & women ages 40-69
- GWAS, biochemistry for all 500k
- Imaging visit (MRI, DXA, carotid, eye) for 100k
- Prospective follow up over many years

Baseline samples

Vacutainer tube	Fractions	Number of aliquots −80°C	Number of aliquots Liquid N_2
EDTA (9 ml) × 2	Plasma	6	2
	Buffy coat	2	2
	Red cells	1	1
LH (PST)	Plasma	3	1
Clot activator (SST)	Serum	3	1
ACD	DMSO blood	–	2
EDTA (4 ml)	Haematology (immediate)	–	–
Urine	Urine	4	2
Total Aliquots		19	11

PST, plasma separation tube; SST, serum separation tube; LH, lithium heparin. Plus Tempus tube (RNA) and saliva



Elliott & Peakman *Int J Epidemiol* 2008; 37: 234-44
Sudlow et al *PLoS Med 2015; 12(3):e1001779*

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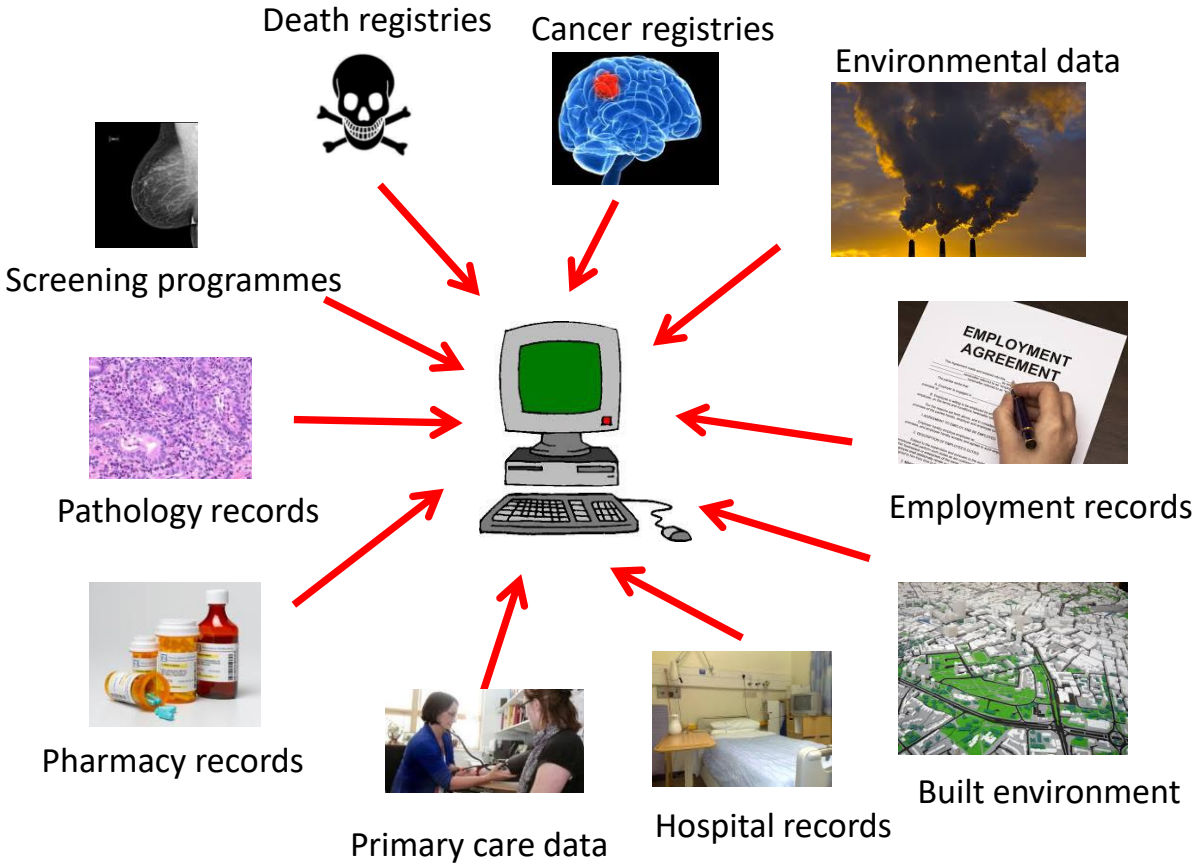
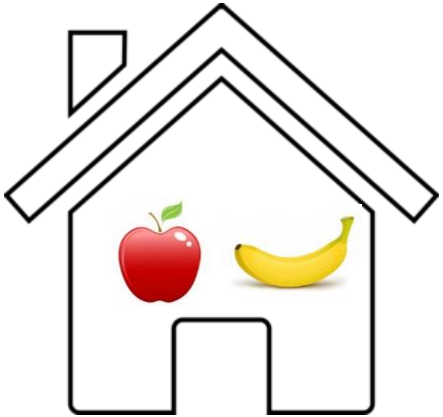
UK Biobank: Record linkage



Courtesy M Landray

The Systems Biology Lesson – Integration Takes Effort



Bio-medical data
Biologists, Clinicians

Bridging skills:
Understanding
Programming
Data types
Metadata
Methodologies
Software

Models
Numerical scientists

Data integration
Models
Hypothesis testing

interpretation

Interdisciplinary
Training and skillset building

Key Takeaways

- New approaches (*omics*) to capitalise on well-phenotyped cohorts and biobanks with long-term follow-up
- New insights on pathways and mechanisms linking environmental exposures to disease (***exposome***)
- Integrating, analysing and obtaining new knowledge from this wealth of information – computational challenge!
- ***Requires new ways of working and integrated inter-disciplinary approaches***