Northwestern Medicine®

Advancing Nutrition Research Through Systems Epidemiology

The National Academies of
Sciences • Engineering • Medicine

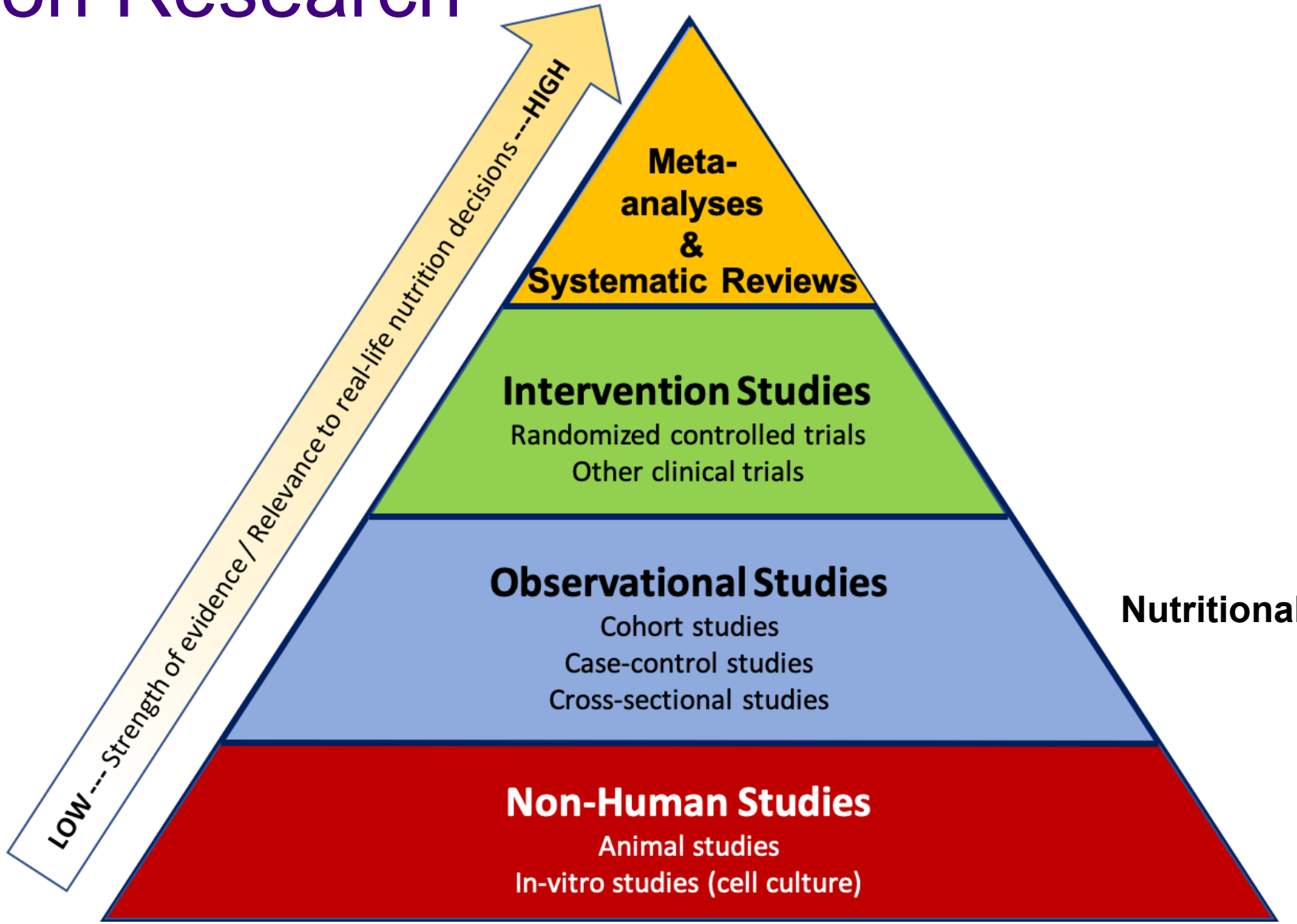
Marilyn Cornelis, PhD

No Disclosures

Today's Talk

1. Traditional vs Systems epidemiology
2. Applied systems epidemiology & nutrition
3. Future: Personalized nutrition research

Nutrition Research



Nutritional Epidemiology

Limitations of Nutritional Epidemiology

- Classical limitations (measurement error, confounding)
  - Subjective diet data collection
  - Limitation in food composition tables
  - Unclear diet-disease temporal relationship
- Complex nature of diet (chemicals, foods, diet patterns)
  - Food matrix interactions (vitamin C & iron, fiber & carotenoids, cooking)
- Variation in dietary intake and physiological exposure
  - within-person, between-person, between-populations
- No insight to causality or mechanisms

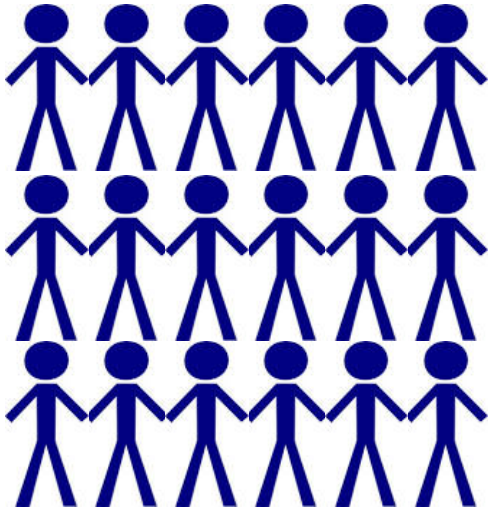
the “OMICs”

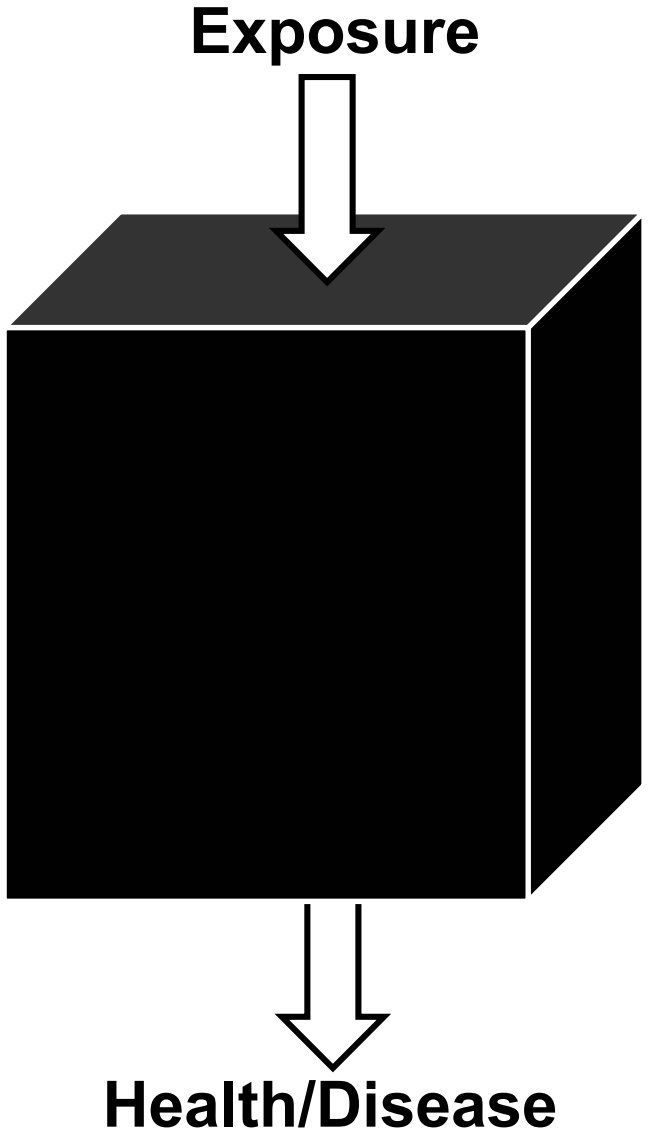
The collective technologies used to explore the roles, relationships, and actions of the various types of molecules that make up the cells of an organism

high-throughput
‘global view’
hypothesis generating

Traditional Epidemiology

clinical & self-report data





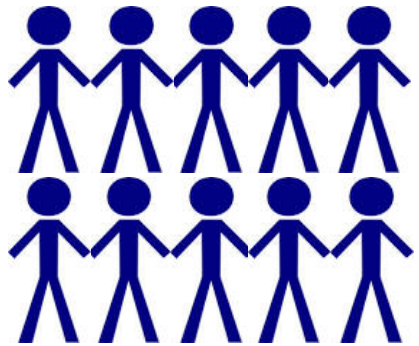
Cornelis & Hu. *Curr Nutr Rep*. 2013

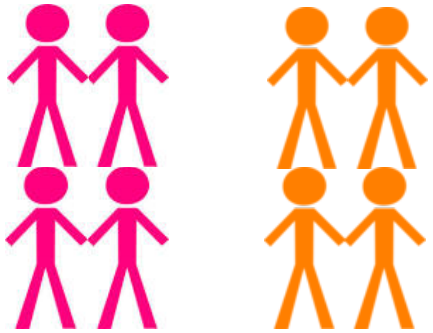
‘Systems’ Epidemiology

Insight to mechanisms

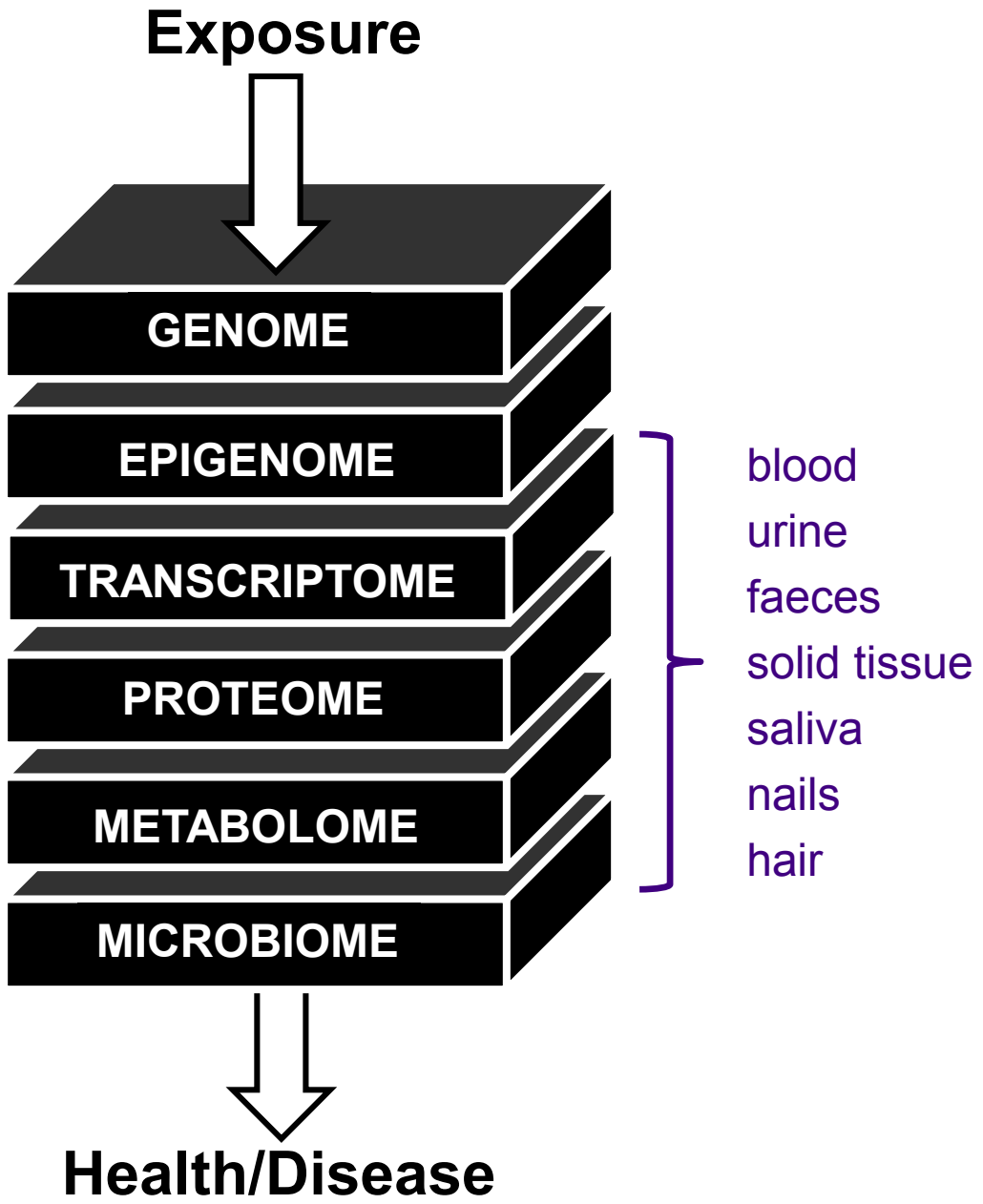
Informs nutritional guidelines & novel prevention strategies

clinical & self-report data





personalized nutrition



Cornelis & Hu. *Curr Nutr Rep*. 2013

biobank uk

Improving the health of future generations

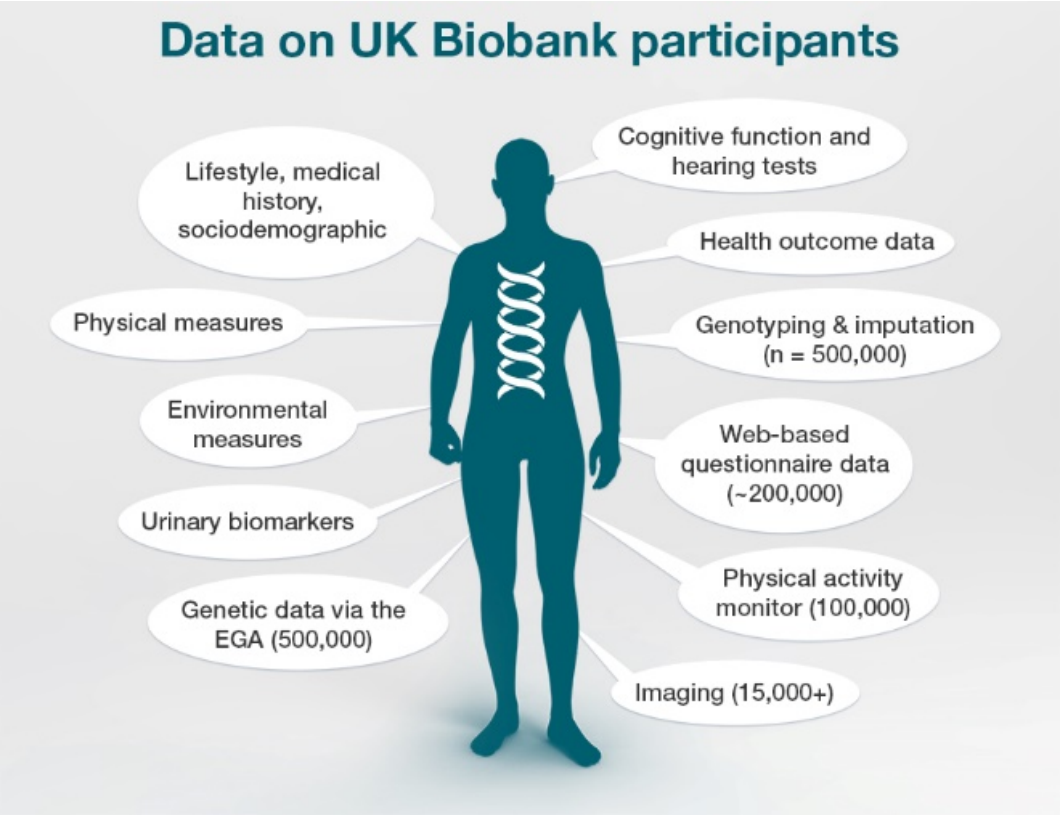


Figure sources: https://www.ebi.ac.uk/about/news/feature-story/biobanks-genetic-data-demand
Naomi Allen, Senior Epidemiologist, UK Biobank (July 2017)

2006-2010

500,000+ participants aged 37-73 y 22 centers across England, Wales and Scotland

touchscreen questionnaires on sociodemographic factors, lifestyle and medical history

in-person questionnaire, physical assessment, and biospecimen collection

on-line data collection

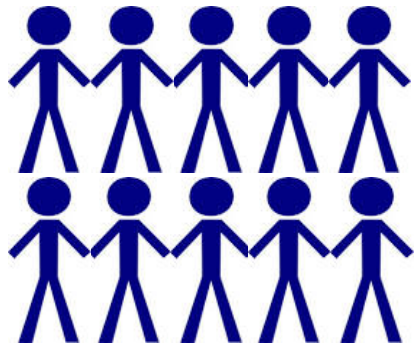
continued follow-up

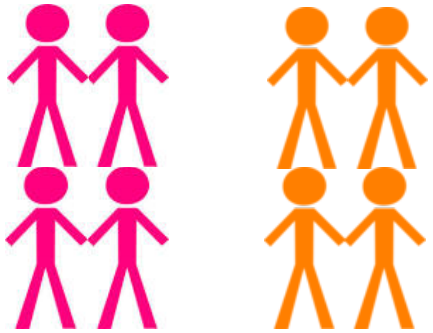
‘Systems’ Epidemiology

Insight to mechanisms

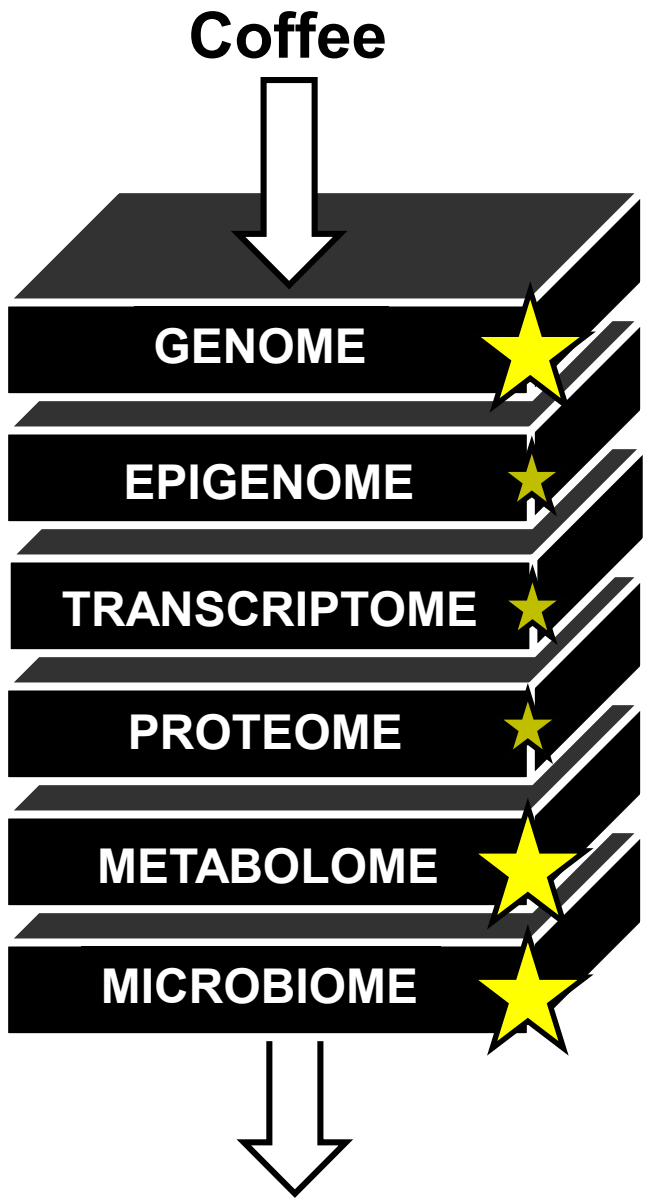
Informs nutritional guidelines & novel prevention strategies

clinical & self-report data





personalized coffee guidelines



Cornelis. *Curr Opin. Lipidol.* 2015

Key Themes from Observational Studies of Coffee and Health
Poole et al, BMJ 2017

All cause mortality
CVD-mortality
Incident CVD
Beneficial: Greatest risk reduction with 3 to 5 cups/d

Cancer
Increased risk for lung cancer
No relationship or dose-response risk reduction for other cancers

Liver and gastrointestinal outcomes
Metabolic disease
Neurological outcomes
Beneficial: dose-response risk reduction

Antenatal exposure to coffee: No relationship or increased risk

Musculoskeletal outcomes
Potential risk among women but not men

Renal outcomes
Gynecological outcomes
No relationship

To Your Health

The Washington Post

Good news: It's totally fine to drink lots (and lots) of coffee. The government just said so

Measuring Coffee Intake

black	green		arabica	robusta
60-90	35-70	← mg/8oz →	100-170	185-265

caffeine

catechins
theaflavins
tannins
l-theanine

caffeine

chlorogenic acids
melanoidins
trigonelline
diterpenes

Individuals vary in their physiological exposure and response to coffee

Exposure: absorption, distribution, metabolism, excretion

caffeine: $T_{1/2}$ of 2-12 hours

pharmacokinetics

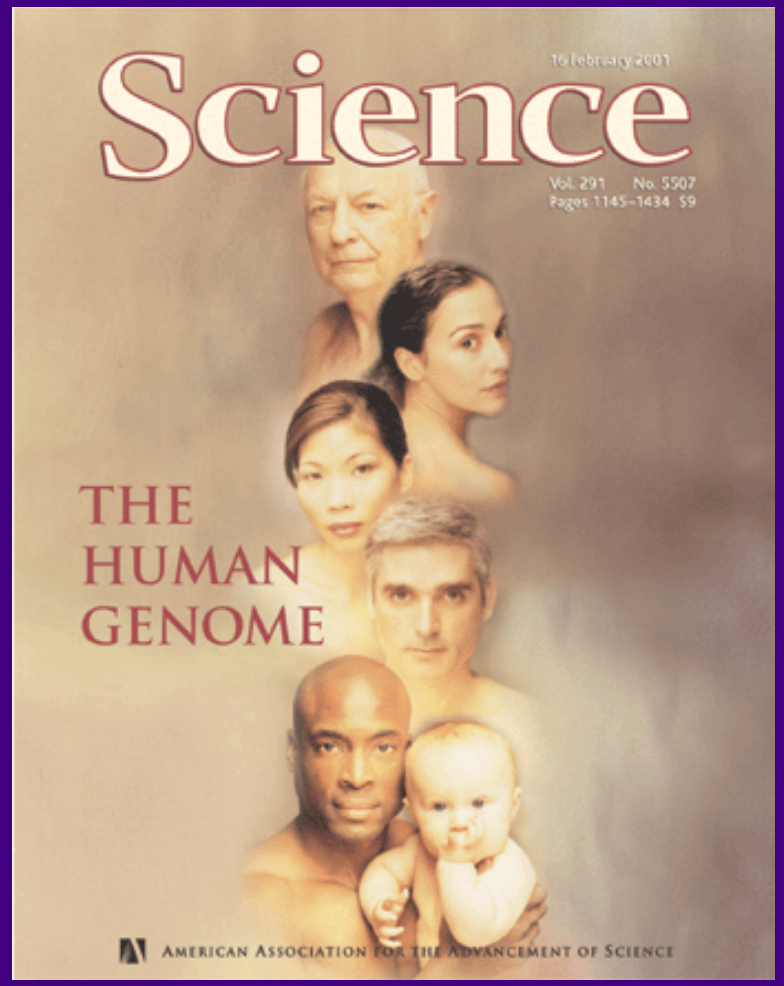
Response: i.e psychostimulant effects




pharmacodynamics

Cornelis, Coffee Intake. In: Nutrigenetics and Nutrigenomics. Prog Mol Biol Transl Sci, 2012

Human Genetics



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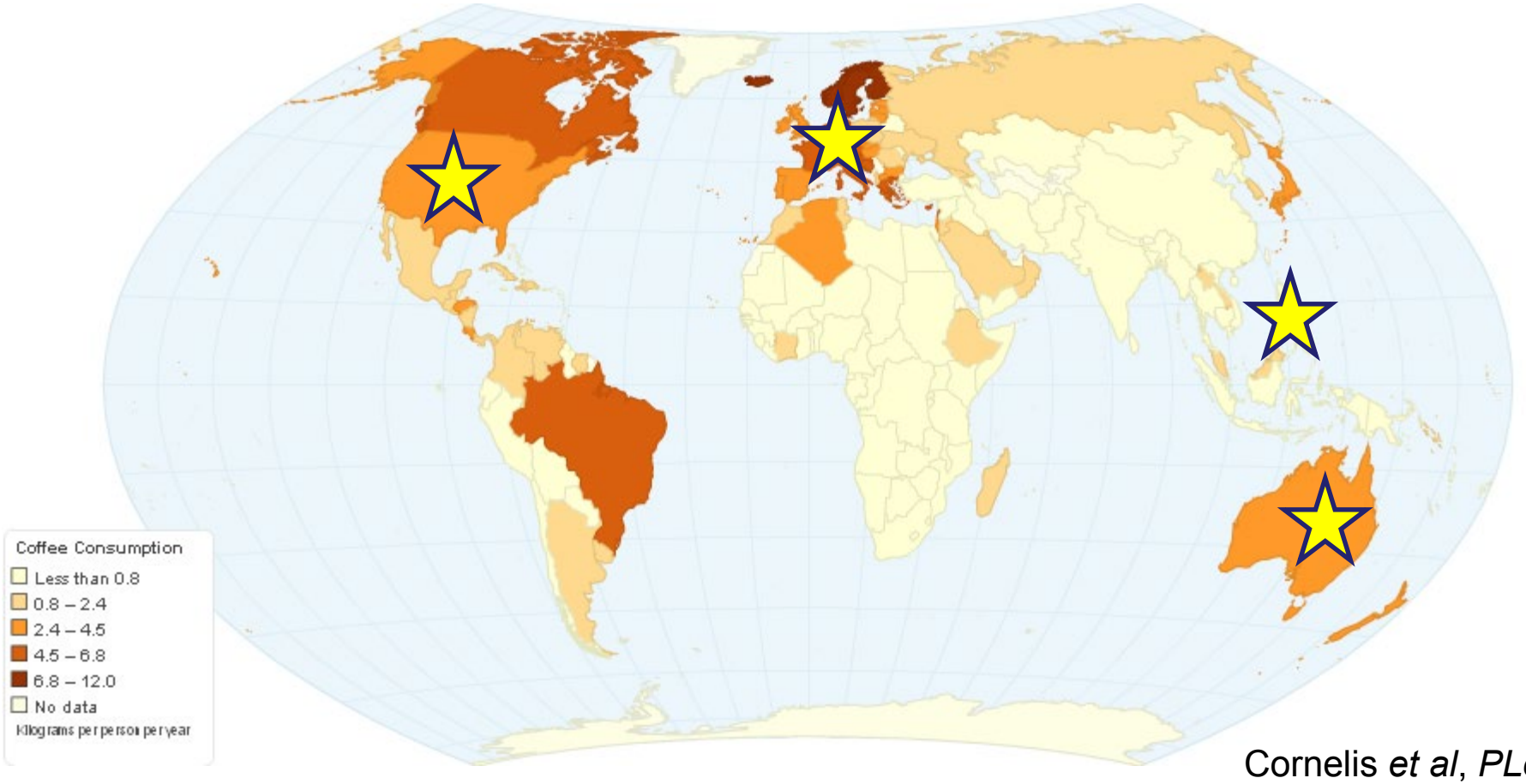
Genome-wide association study (GWAS)

GWAS OF COFFEE & CAFFEINE DRINKING BEHAVIOR
GWAS OF CAFFEINE METABOLITES



Cornelis *et al*, *PLoS Genetics,* 2010
Cornelis *et al*, *Mol Psychiatry,* 2015
Cornelis *et al*, *Hum Mol Genetics*, 2016
Nakagawa et al, *Scientific Rep*, 2018
Zhong *et al, Hum Mol Genetics*, 2019
Jia et al, *BMC Genet* 2019

GWAS summary ↑ ↓

	Candidate Gene	Effect of reference allele	
		caffeine metabolites	caffeine & coffee intake
pharmacokinetics	*AHR*		
	CYP1A2		
	POR		
	CYP2A6		
	ABCG2		
pleiotropic	*GCKR*		
	MLXIPL		
pharmacodynamics	*BDNF*		
	SLC6A4		
	ADORA2A		
	OR8U8		
pleiotropic	*SEC16B*		
	TMEM18		
	MC4R		
	AKAP6		

JOURNAL OF THE EXPERIMENTAL ANALYSIS OF BEHAVIOR 1986, 45, 133–148 NUMBER 2 (MARCH)

HUMAN COFFEE DRINKING: MANIPULATION OF CONCENTRATION AND CAFFEINE DOSE

ROLAND R. GRIFFITHS, GEORGE E. BIGELOW, IRA A. LIEBSON, MARY O'KEEFFE, DAVID O'LEARY, AND NASON RUSS

THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE

In a residential research ward coffee drinking was studied in 9 volunteer human subjects with histories of heavy coffee drinking. A series of five experiments was undertaken to characterize ad-libitum coffee consumption and to investigate the effects of manipulating coffee concentration, caffeine dose per cup, and caffeine preloads prior to coffee drinking. Manipulations were double-blind and scheduled in randomized sequences across days. When cups of coffee were freely available, coffee drinking tended to be rather regularly spaced during the day with intercup intervals becoming progressively longer throughout the day; experimental manipulations showed that this lengthening of intercup intervals was not due to accumulating caffeine levels. Number of cups of coffee consumed was an inverted U-shaped function of both coffee concentration and caffeine dose per cup; however, coffee-concentration and dose-per-cup manipulations did not produce similar effects on other measures of coffee drinking (intercup interval, time to drink a cup, within-day distribution of cups). Caffeine preload produced dose-related decreases in number of cups consumed. As a whole, these experiments provide some limited evidence for both the suppressive and the reinforcing effects of caffeine on coffee consumption. Examination of total daily coffee and caffeine intake across experiments, however, provides no evidence for precise regulation (i.e., titration) of coffee or caffeine intake.

Key words: coffee, caffeine, drug self-administration, tremor, subjective effects, coffee drinking, humans

How can we use these genetic findings?

risk assessment
intervention design

biological & mechanistic insight

food & drug manufacturing & marketing

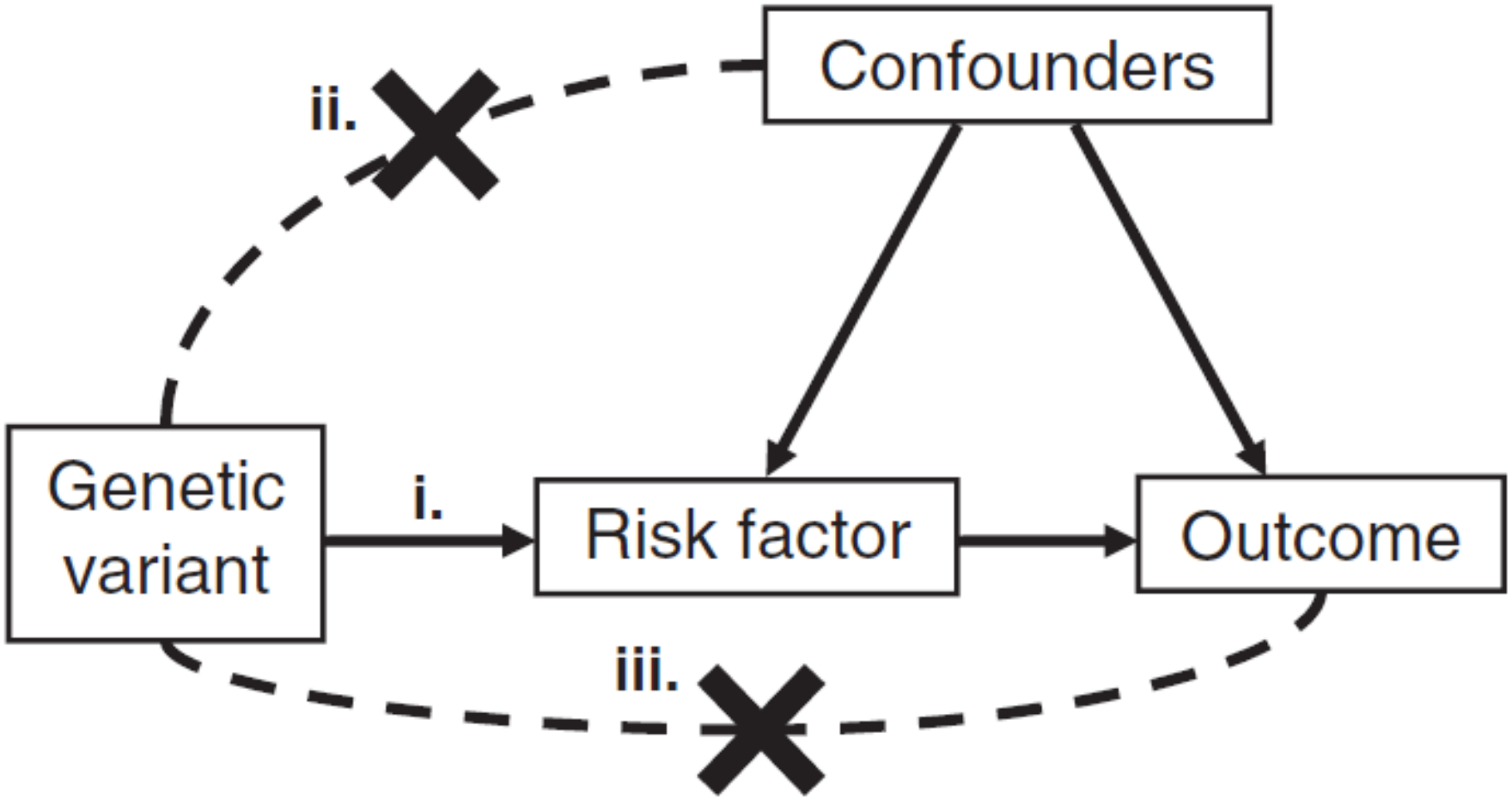
GENETICALLY WIRED

YOUR DNA AFFECTS HOW YOUR BODY REACTS TO CAFFEINE.
GET TESTED WITH **23ANDME.COM** TO LEARN ABOUT YOUR LIKELY RESPONSE

23andMe

Mendelian Randomization

Assumptions



Burgess et al, Epidemiolgoy 2017

nutrients

MDPI

Review

Mendelian Randomization Studies of Coffee and Caffeine Consumption

Marilyn C. Cornelis [1,*] and Marcus R. Munafo [2]

Applications

- 15+ published MR studies

  T2D, CVD, Alzheimer's, Parkinson's, gout, cancers, osteoarthritis, sleep disturbances, substance use

- Most studies provide no consistent support for a causal role

nutrients

MDPI

Review

Mendelian Randomization Studies of Coffee and Caffeine Consumption

Marilyn C. Cornelis [1,*] and Marcus R. Munafo [2]

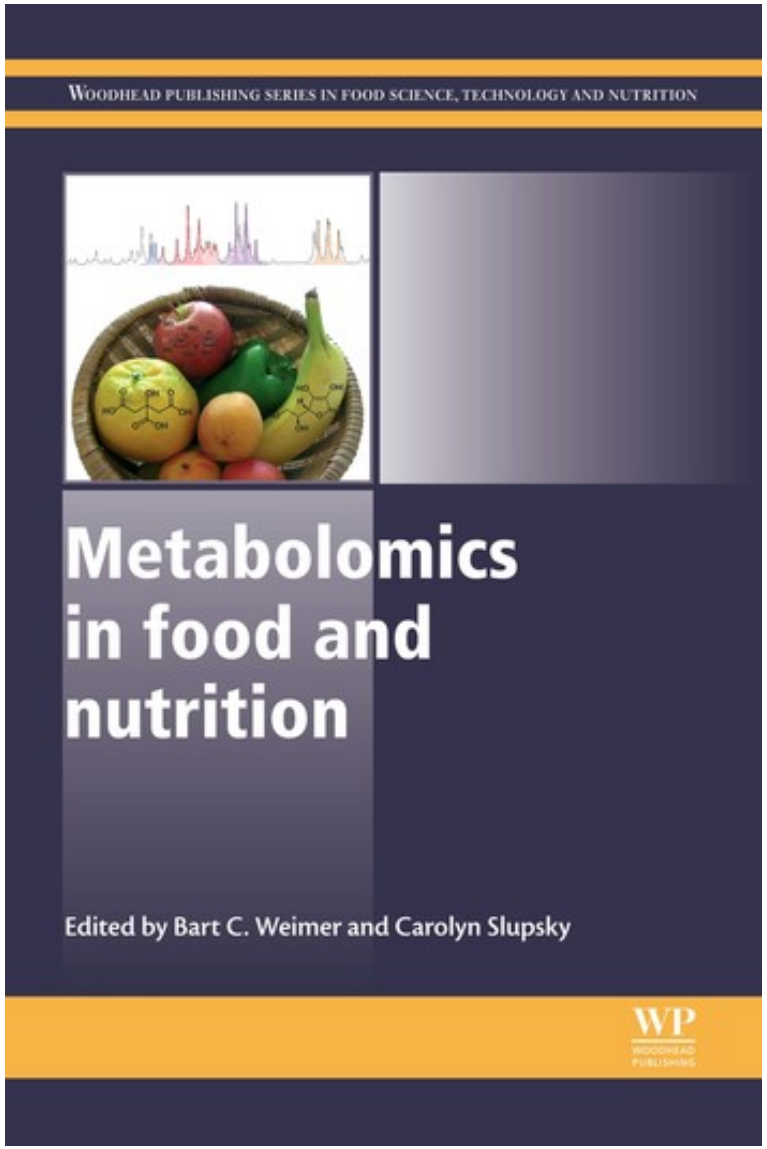
Challenges

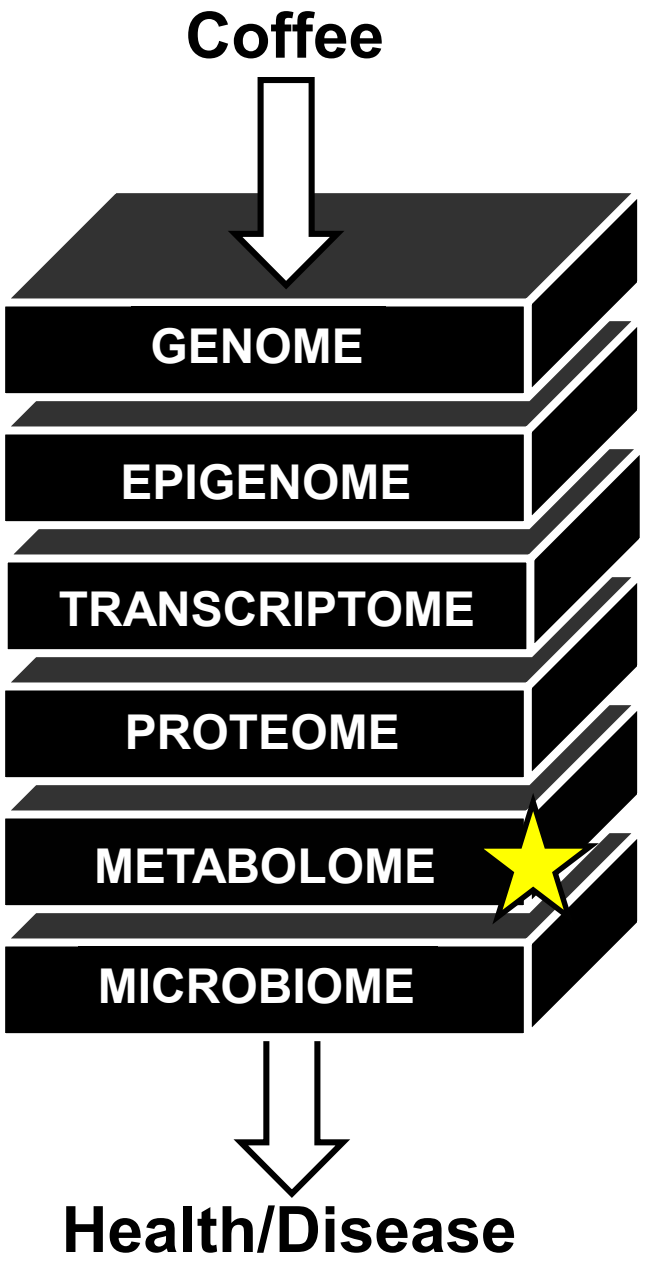
- Trait heterogeneity

  AHR & CYP1A2 SNPs ↑ caffeine/coffee behavior, ↓ caffeine metabolites
  ↑ decaf coffee (former regular drinkers?)
  ↑ black coffee (*submitted*)
  ↓ sugar sweetened beverages, water (UK Biobank)

- Power
- Pleiotropy
- Others: collider bias, handling potential nonlinear effects, interpretation

‘Systems’ Epidemiology





Effects of coffee consumption on subclinical inflammation and other risk factors for type 2 diabetes: a clinical trial[1–3]

Kerstin Kempf, Christian Herder, Iris Erlund, Hubert Kolb, Stephan Martin, Maren Carstensen, Wolfgang Koenig, Jouko Sundvall, Siamak Bidel, Suvi Kuha, and Jaakko Tuomilehto

Am J Clin Nutr, 2010

Characteristics (N=47, high T2D risk)	
age, years	54 (9)
female, n (%)	36 (77)
BMI, kg/m^2	29 (5)
waist circumference, cm	98 (11)
SBP, mm Hg	141 (15)
DBP, mm Hg	90 (9)
current smoker, n (%)	2 (4)
coffee intake, 150-ml cups/d	4 (2)

3-stage clinical trial

1 month: 0 cups/d (blood draw)

1 month: 4 cups/d (blood draw)

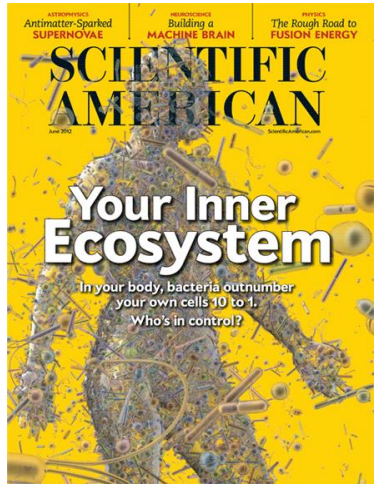
1 month: 8 cups/d (blood draw)

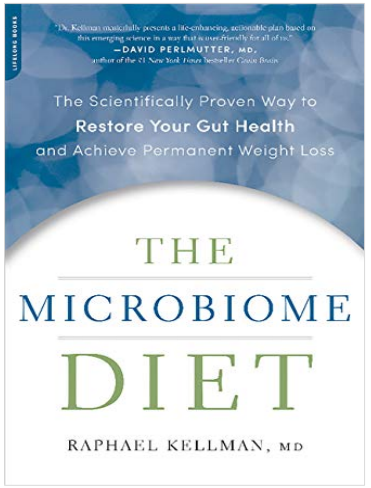
Plasma metabolite profiling (UPLC-MS/MS) → 733 metabolites

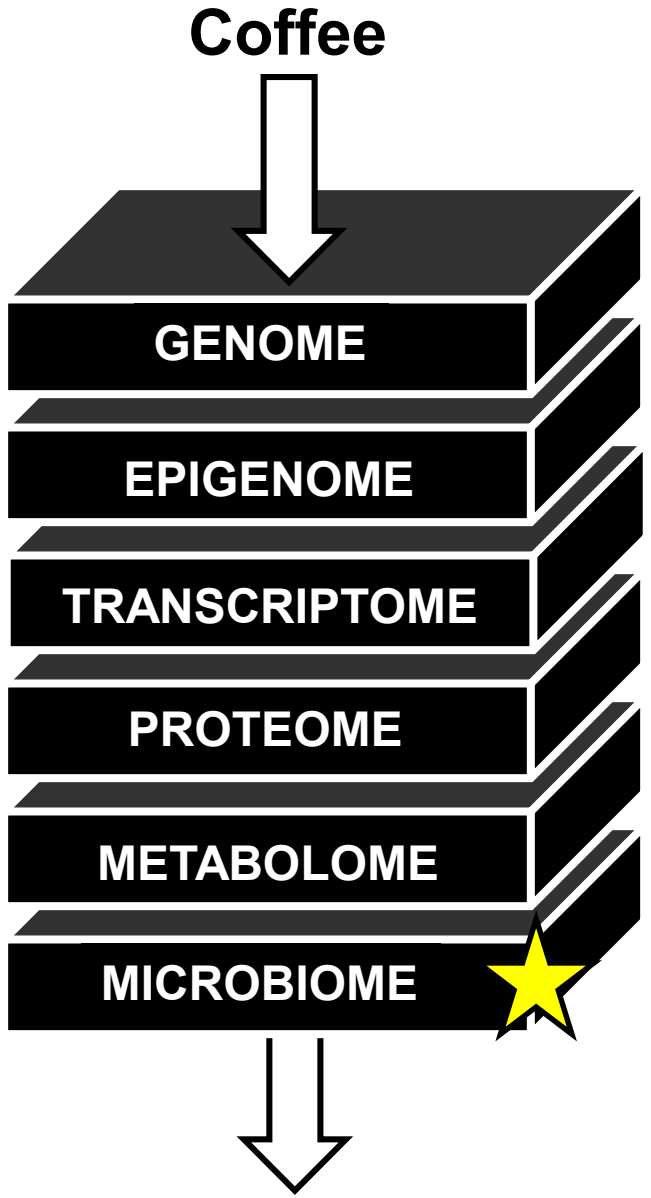
Cornelis et al. *J Internal Med* 2016

Pathway	Subpathway	↑	↓
Amino Acid (15)	Creatine Metabolism	2	
	Histidine Metabolism	1	1
	Leucine, Isoleucine and Valine Metabolism	1	
	Methionine, Cysteine, SAM and Taurine Metabolism	2	
	Polyamine Metabolism	2	
	Tryptophan Metabolism	2	1
	Tyrosine Metabolism	1	
	Urea cycle; Arginine and Proline Metabolism		1
Carbohydrate (2)	Aminosugar Metabolism	1	
	Glycolysis, Gluconeogenesis, and Pyruvate Metabolism		1
Cofactors and Vitamins (1)	Nicotinate and Nicotinamide Metabolism	1	
Energy (2)	Oxidative Phosphorylation	1	
	TCA Cycle	1	
Lipid (24)	Diacylglycerol		1
	❖ **Endocannabinoid**		4
	❖ **Fatty Acid Metabolism (Acyl Choline)**		6
	Glycerolipid Metabolism		1
	Phospholipid Metabolism		1
	Polyunsaturated Fatty Acid (n3 and n6)		1
	Secondary Bile Acid Metabolism		1
	Sphingolipid Metabolism	1	
	❖ **Steroid**	3	2
	Sterol	1	1
Nucleotide (4)	Purine Metabolism, (Hypo)Xanthine/Inosine containing	1	
	Purine Metabolism, Adenine containing	1	
	Purine Metabolism, Guanine containing	1	
	Pyrimidine Metabolism, Uracil containing		1
Peptide (2)	Dipeptide Derivative	1	
	Fibrinogen Cleavage Peptide	1	
Xenobiotics (32)	❖ **Benzoate Metabolism**	9	
	Chemical	3	
	Food Component/Plant	6	
	❖ **Xanthine Metabolism**	14	
Unknown (34)	Unknown	23*	10*

‘Systems’ Epidemiology





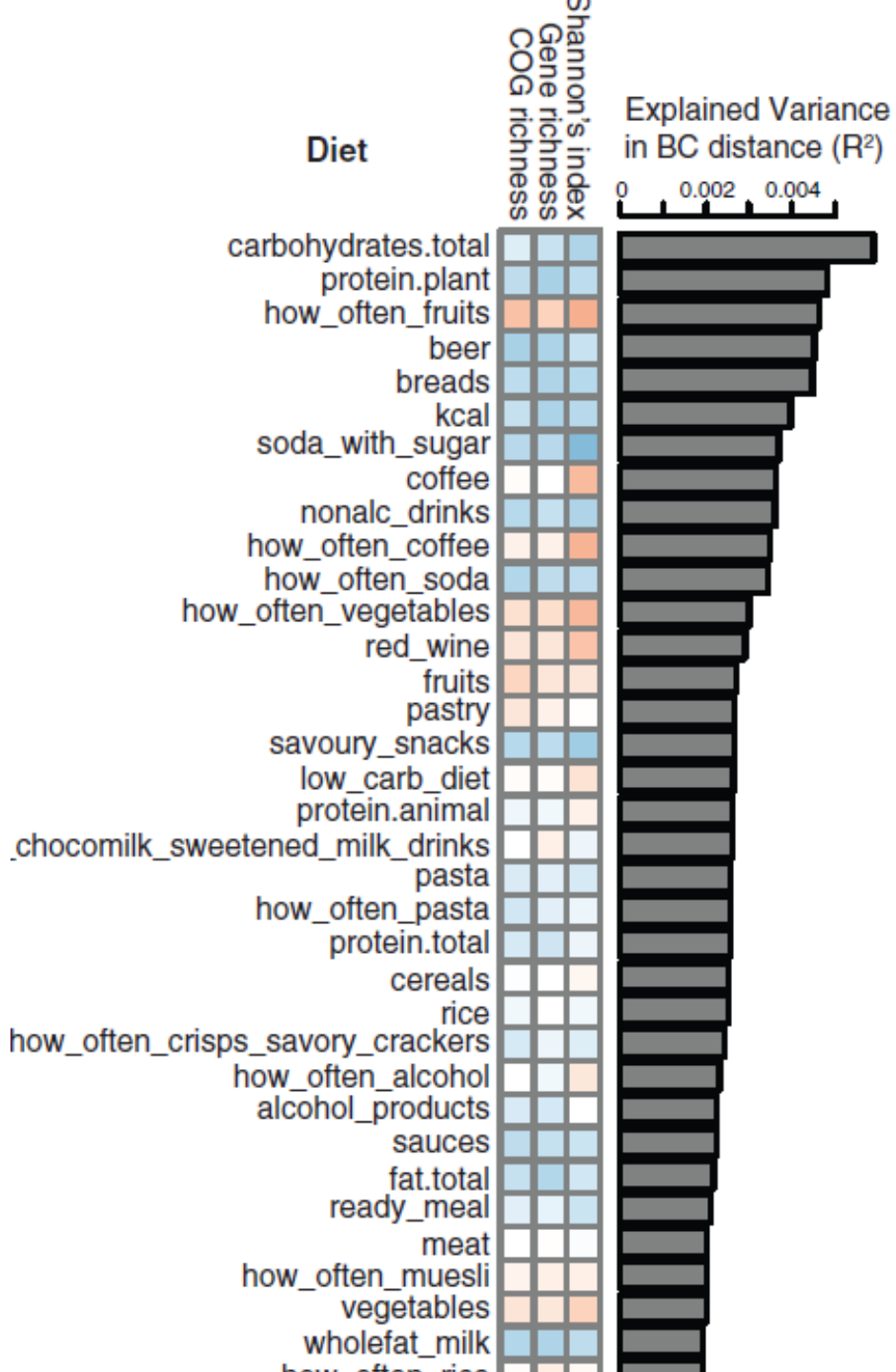


MICROBIOME

Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity

N=1135, LifeLines-DEEP (Netherlands)
Stool samples
207 factors (76 diet)

Coffee
Diversity
Lachnospiraceae
Veillonella parvula
Haemophilus parainfluenzae



Zhernakkova et al, 2016 Science

Personalized (Precision) Nutrition

Develop robust & objective biomarkers of nutrient exposure and response/effect

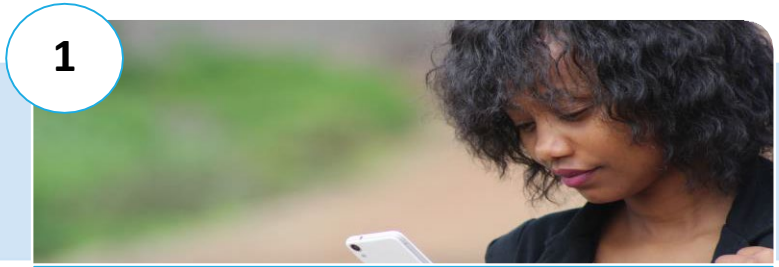
- validate subjective measures of intake
- nutritional status & monitoring
- monitor compliance and individual response
- improve health prediction models
- ‘tools’ for insight to mechanisms linking nutrition to disease

- Promote and maintain optimal health!

Nutrition for Precision Health

National Institutes of Health

1



Examine **baseline diet** in an **observational study** followed by a mixed meal challenge test

10,000 *All of Us* participants

2

Examine responses to 3 short-term intervention diets in free-living **controlled feeding** studies

1,000-2,000 Module 1 participants

3

Examine responses to 3 short-term intervention diets in **domiciled controlled feeding** studies

500-1,000 Module 1 participants

In all 3 modules

- Collect microbiome, physiological, metabolic, behavioral, cognitive, and environmental data, and leverage existing genomic, EHR, and survey data, and conduct mixed meal challenges to model the impact of diet and dietary patterns on physiological responses
- Use machine learning and artificial intelligence to develop predictive algorithms

Acknowledgments

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University of Toronto

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Harvard

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