

Nutritional Epidemiology of Chronic Diseases in the Multi-Omics Era

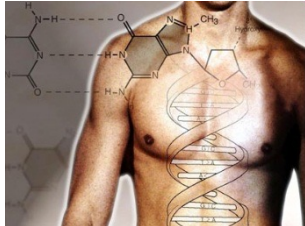
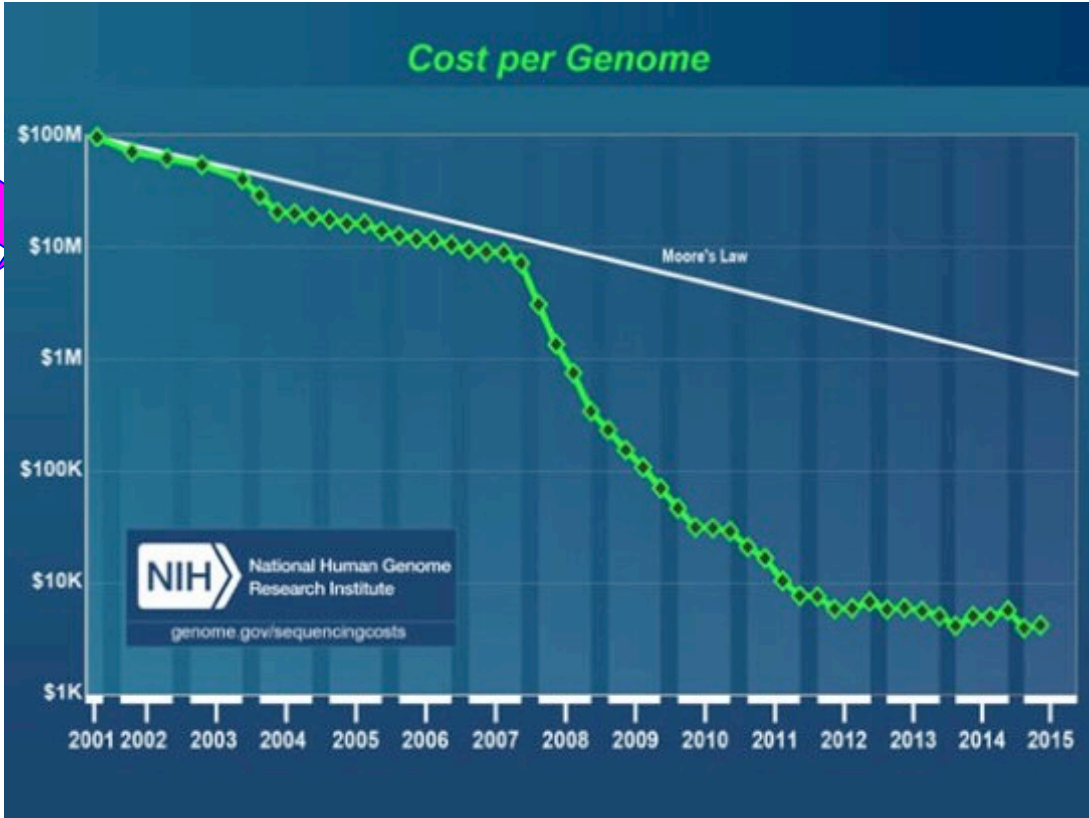
Frank B. Hu, MD, PhD
Professor and Chair
Department of Nutrition
Harvard T.H. Chan School of Public Health
Professor of Medicine
Harvard Medical School

Bio-nomics Family

Genomics



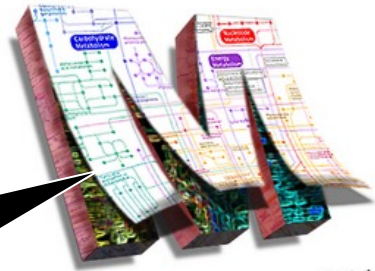
DNA



Phenotypes
Functions



Metabolomics



Metabolites

- ✓ Nucleotides
- ✓ Amino Acids

Genomics and proteomics tell you what might happen, but **metabolomics** tells you what actually did happen!
Bill Lasley, University of California, Davis

Paradigm Shift: From Black Box Epi to Systems Epi

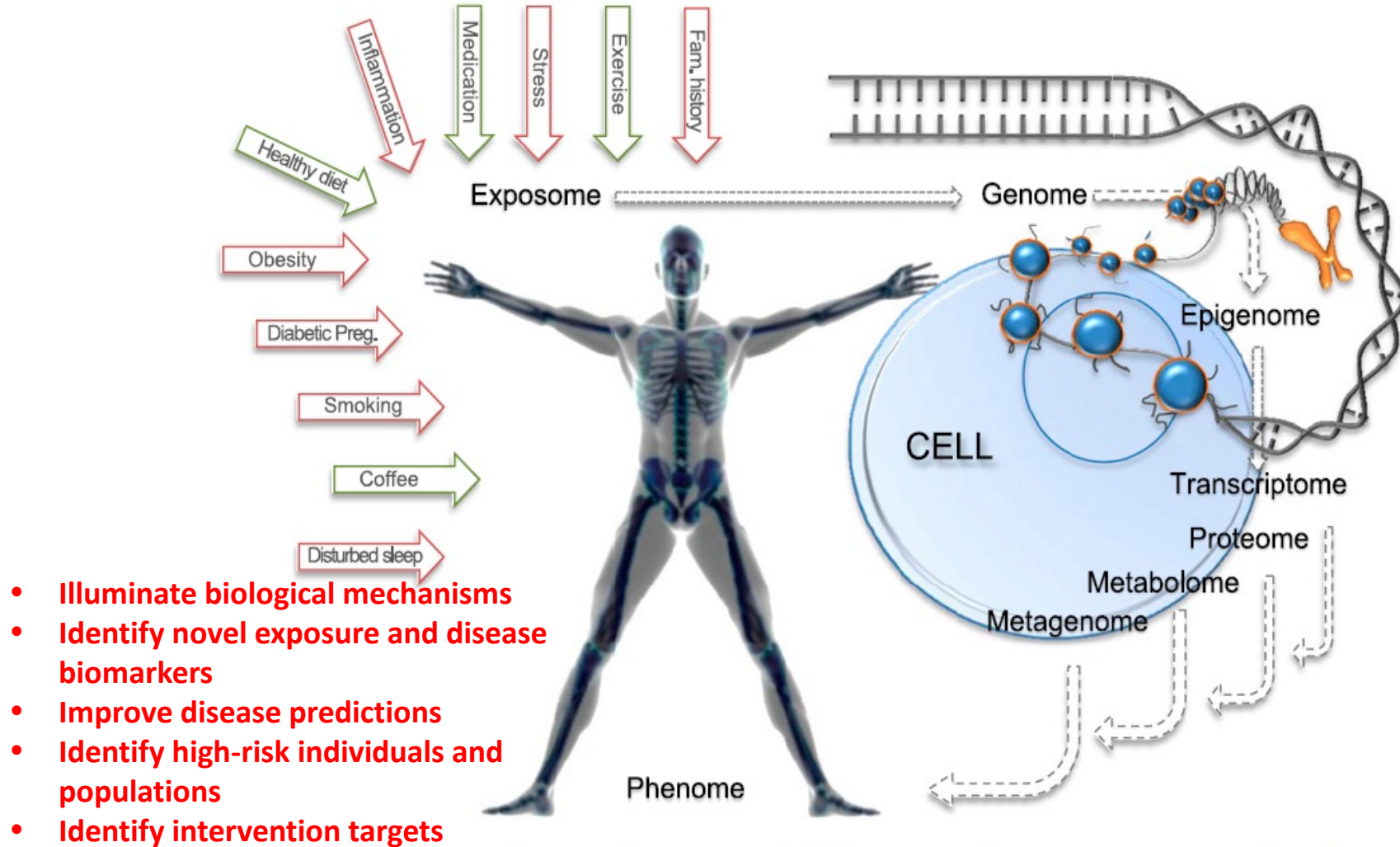
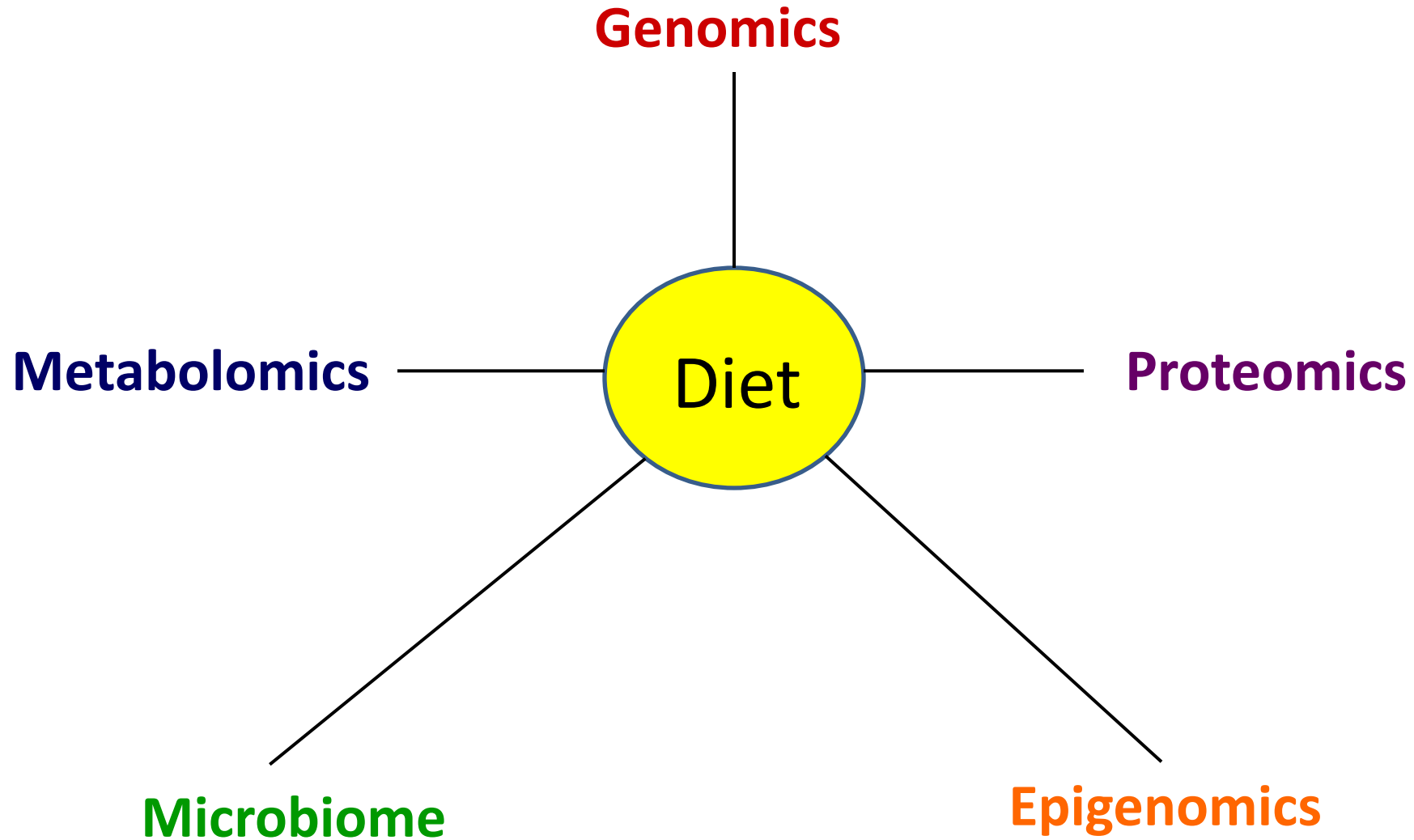
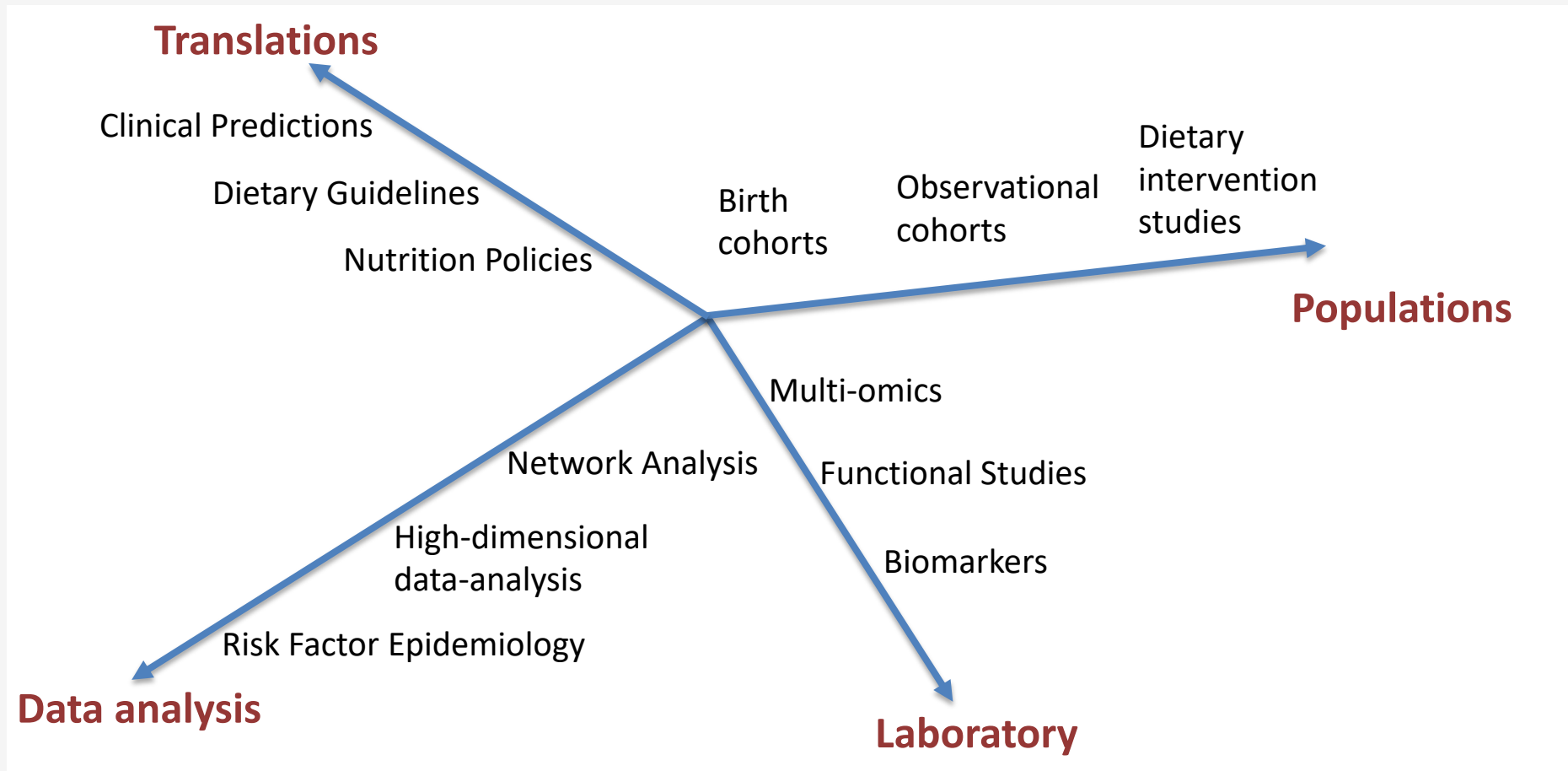


Figure 1—The future of research on stratified diabetes medicine: a systems epidemiology approach to the discovery of interactions between the exposome (all nongenetic elements to which we are exposed) and the quantifiable elements of the human physiome.

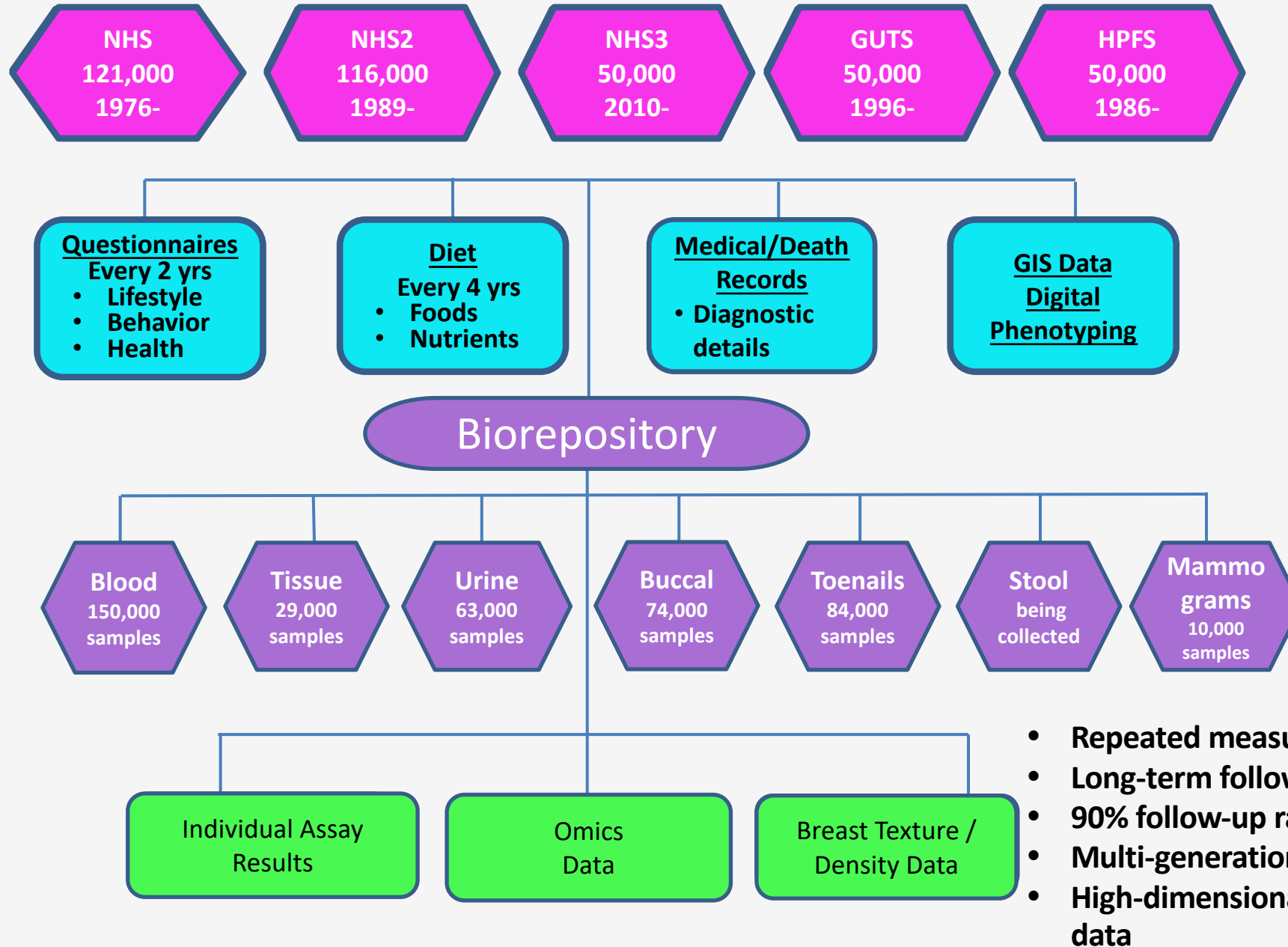
Diet Is Central to -Omics



Integration of Population, Laboratory, Analytical and Translational Approaches to Study Complex Diseases

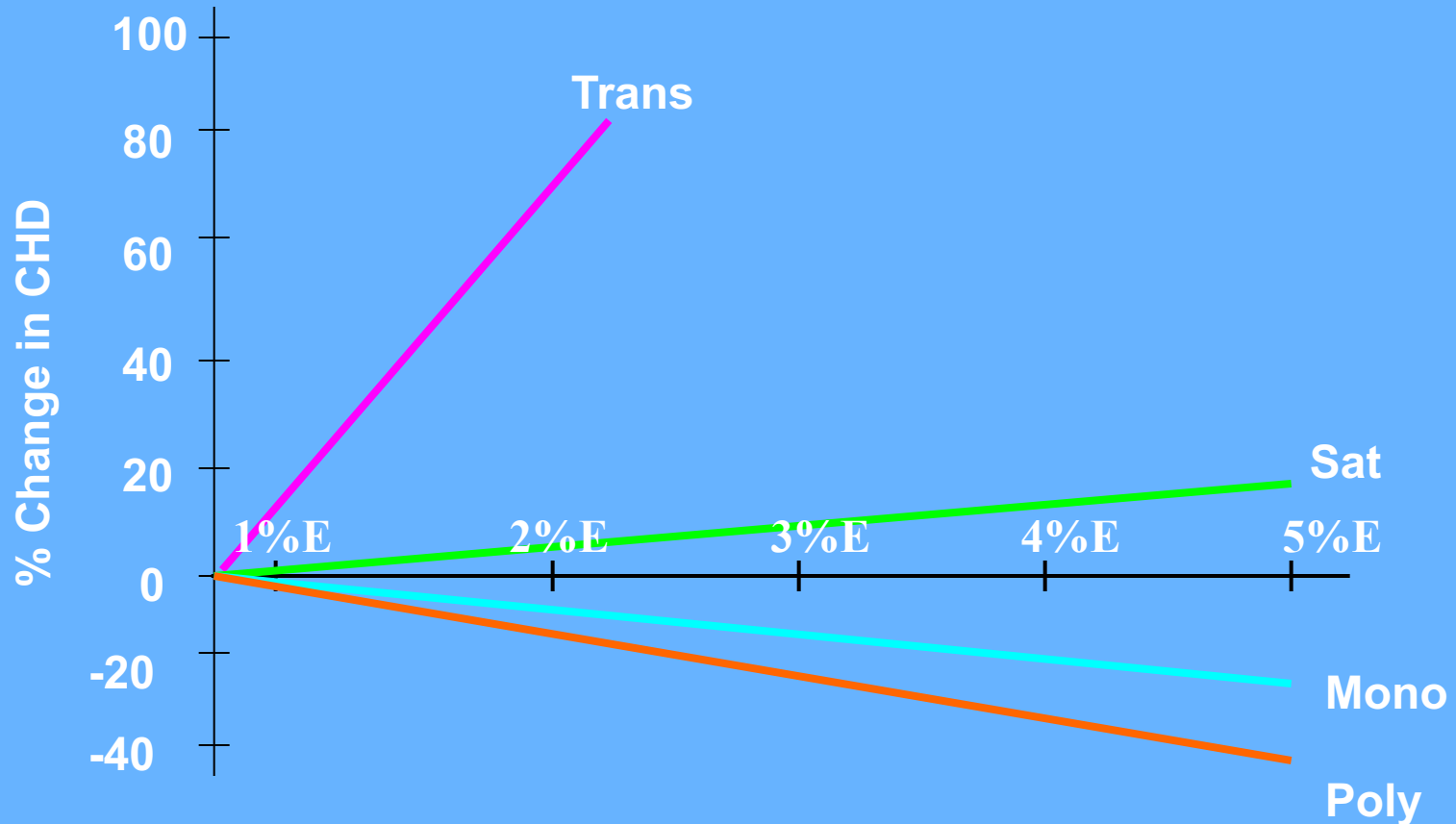


Harvard/BWH Cohorts & Resources



- Repeated measures
- Long-term follow-up
- 90% follow-up rate
- Multi-generational
- High-dimensional data

Types of Fat and Incidence of CHD (Nurses' Health Study)



Hu FB, et al. New Engl J Med 1997

Recent Debate



The New York Times

The Opinion Pages | CONTRIBUTING OP-ED WRITER

Butter Is Back

MARCH 25, 2014



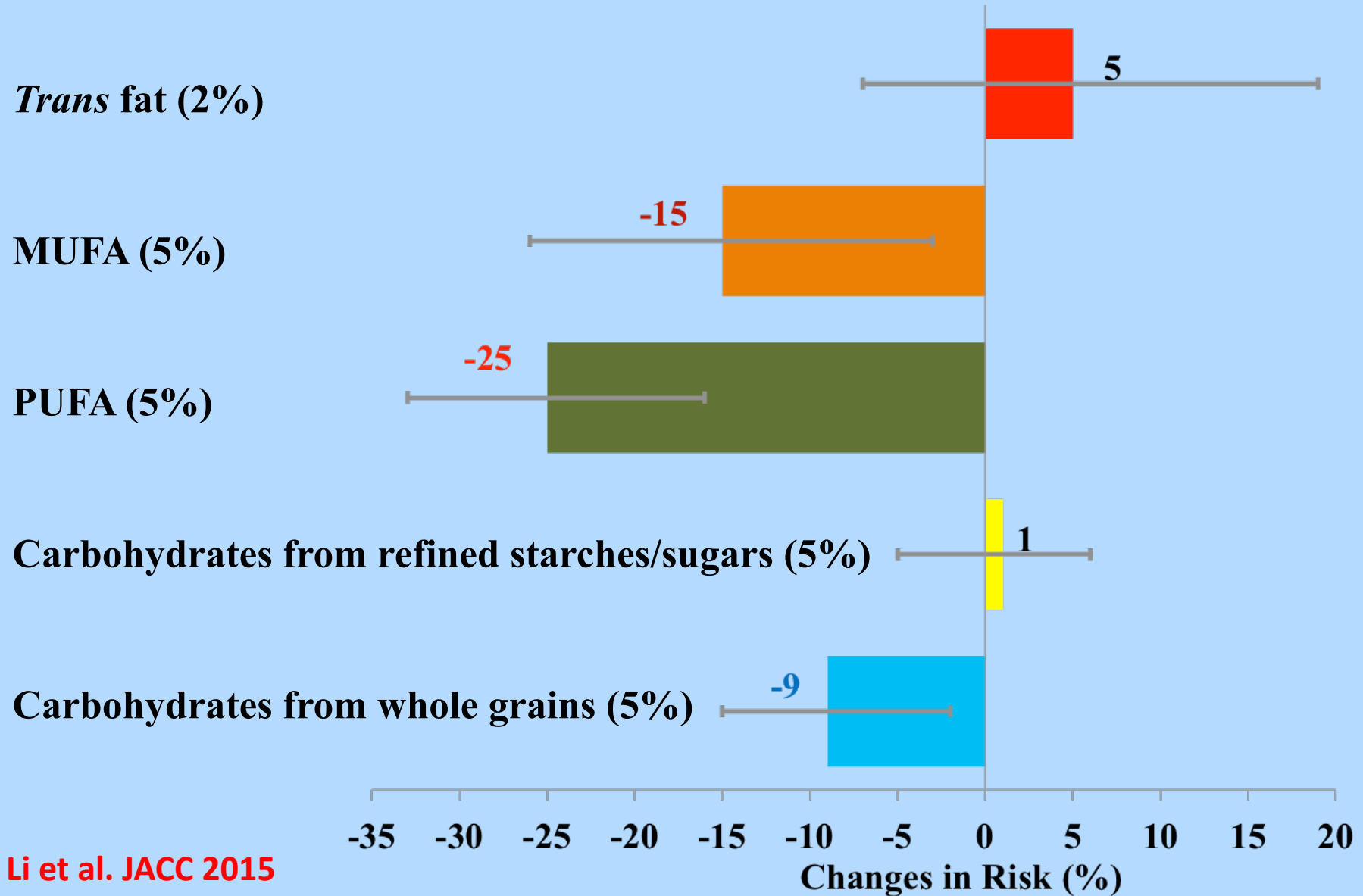
Mark Bittman

Julia Child, goddess of fat, is beaming somewhere. Butter is back, and when you're looking for a few chunks of pork for a stew, you can resume searching for the best pieces — the ones with the most fat. Eventually, your friends will stop glaring at you as if you're trying to kill them.

That the worm is tur

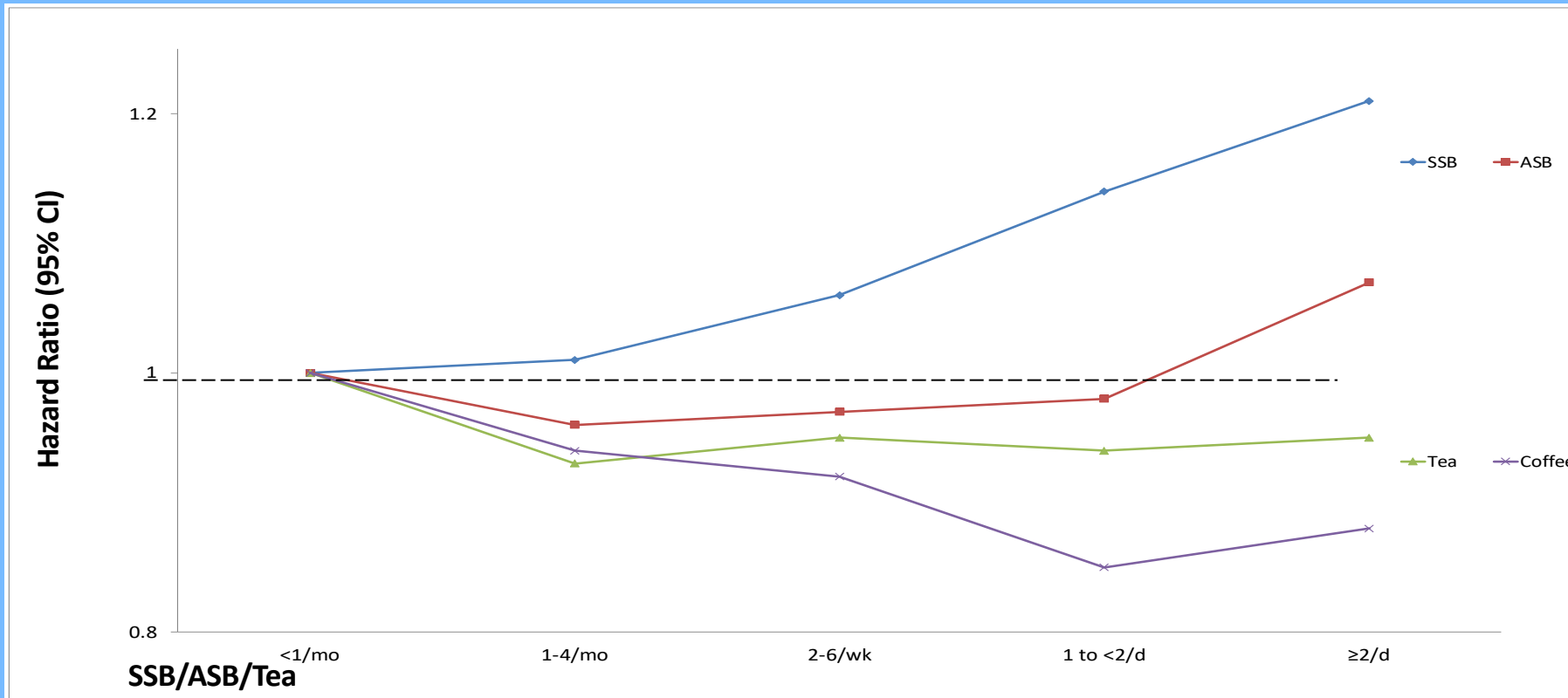


Isocaloric substitution of SFA by equivalent energy from



Beverage consumption in relation to total mortality

(n = 118,316 men and women with 36,436 deaths)



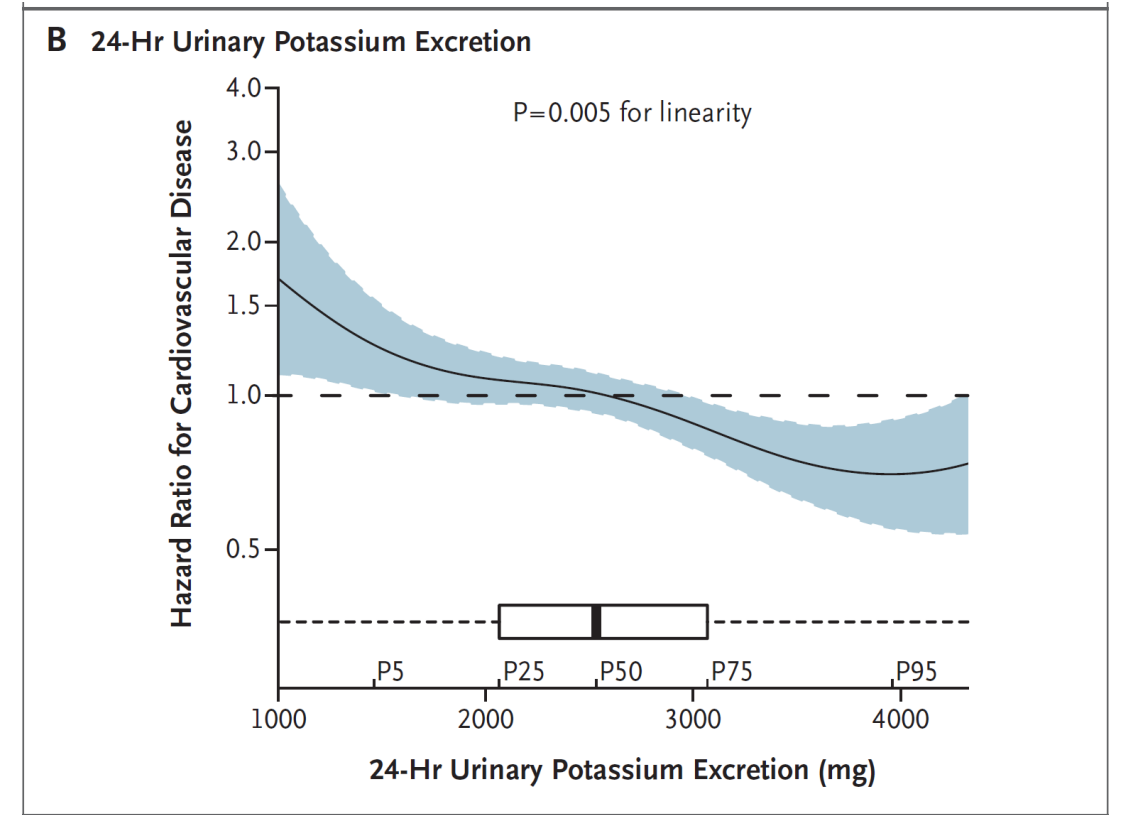
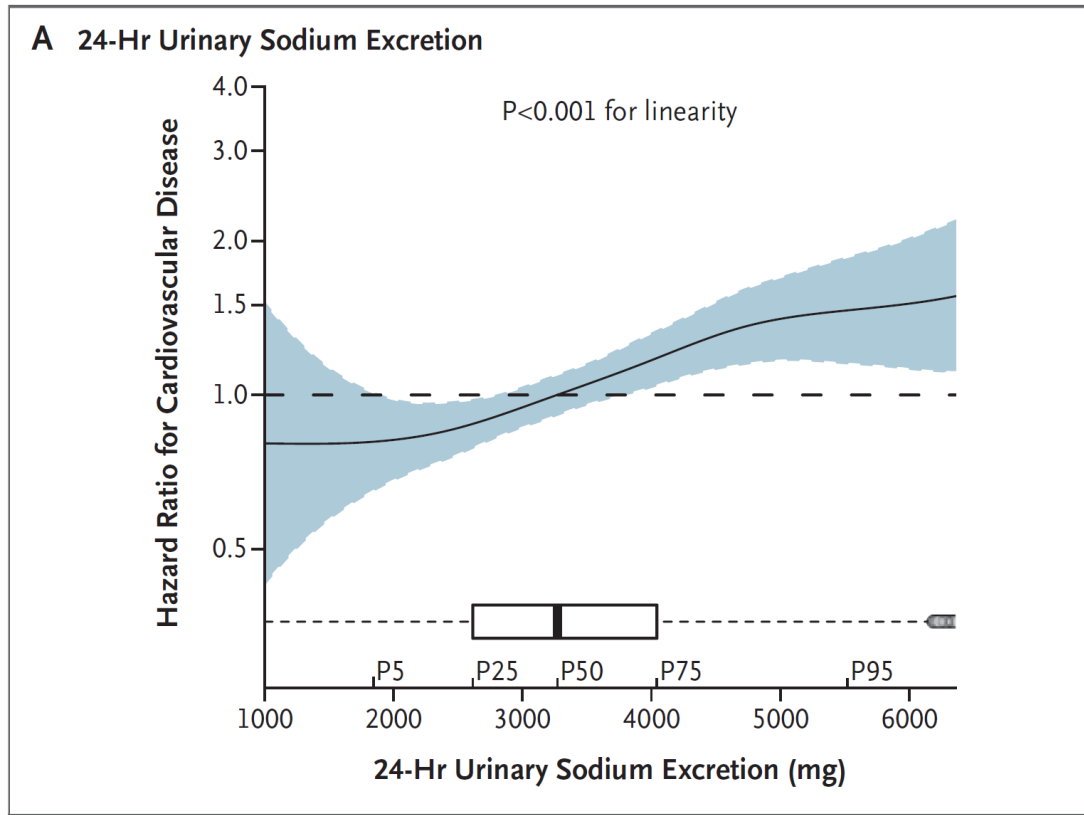
coffee No-coffee =<1 cup/d 1.1-3 cups/d 3.1-5 cups/d >5 cups/d

Malik VS et al. Circulation 2019; Ding M et al. Circulation 2015

ORIGINAL ARTICLE

24-Hour Urinary Sodium and Potassium Excretion and Cardiovascular Risk

Yuan Ma, Ph.D., Feng J. He, Ph.D., Qi Sun, M.D., Sc.D., Changzheng Yuan, Sc.D.,
Lyanne M. Kieneker, Ph.D., Gary C. Curhan, M.D., Sc.D.,
Graham A. MacGregor, M.D., Stephan J.L. Bakker, M.D., Ph.D.,
Norm R.C. Campbell, M.D., Molin Wang, Ph.D., Eric B. Rimm, Sc.D.,
JoAnn E. Manson, M.D., Dr.P.H., Walter C. Willett, M.D., Dr.P.H.,
Albert Hofman, M.D., Ph.D., Ron T. Gansevoort, M.D., Ph.D.,
Nancy R. Cook, Sc.D., and Frank B. Hu, M.D., Ph.D.



Higher 24h urinary sodium and potassium excretion and CVD risk

Home


Research

Association of changes in red meat consumption with total and cause specific mortality among US women and men: two prospective cohort studies

BMJ 2019 ;365 doi: <https://doi.org/10.1136/bmj.l2110> (Published 12 June 2019)

Cite this as: *BMJ* 2019;365:l2110

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- Responses
- Peer review

Yan Zheng , professor^{1 2 3}, Yanping Li, research scientist³, Ambika Satija, research fellow³, An Pan, professor⁴, Mercedes Sotos-Prieto, assistant professor^{3 5 6 7}, Eric Rimm, professor^{3 8 9}, Walter C Willett, professor^{3 8 9}, Frank B Hu, professor^{3 8 9}

> *Diabetes Care*. 2018 May;41(5):1049-1060. doi: 10.2337/dc17-1992. Epub 2018 Mar 12.

Meat Cooking Methods and Risk of Type 2 Diabetes: Results From Three Prospective Cohort Studies

Gang Liu¹, Geng Zong¹, Kana Wu¹, Yang Hu¹, Yanping Li¹, Walter C Willett^{1 2 3}, David M Eisenberg¹, Frank B Hu^{1 2 3}, Qi Sun^{4 2}

Affiliations + expand

PMID: 29530926 PMCID: [PMC5911789](https://pubmed.ncbi.nlm.nih.gov/29530926/) DOI: [10.2337/dc17-1992](https://doi.org/10.2337/dc17-1992)

Free PMC article

This Issue

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Original Investigation

FREE

October 2016

Association of Animal and Plant Protein Intake With All-Cause and Cause-Specific Mortality

Mingyang Song, MD, ScD^{1,2}; Teresa T. Fung, ScD^{2,3}; Frank B. Hu, MD, PhD^{2,4,5}; et al

> Author Affiliations | Article Information



Original Investigation

Long-Term Changes in Gut Microbial Metabolite Trimethylamine N-Oxide and Coronary Heart Disease Risk

Yoriko Heianza RD, PhD^a, Wenjie Ma MD, PhD^b, Joseph A. DiDonato PhD^c, Qi Sun MD, ScD^{d e}, Eric B. Rimm ScD^{d e f}, Frank B. Hu MD, PhD^{d e f}, Kathryn M. Rexrode MD, MPH^{e g h}, JoAnn E. Manson MD, DrPh^{e f g}, Lu Qi MD, PhD^{a d e}

ORIGINAL ARTICLE

Association of Nut Consumption with Total and Cause-Specific Mortality

Ying Bao, M.D., Sc.D., Jiali Han, Ph.D., Frank B. Hu, M.D., Ph.D., Edward L. Giovannucci, M.D., Sc.D., Meir J. Stampfer, M.D., Dr.P.H., Walter C. Willett, M.D., Dr.P.H., and Charles S. Fuchs, M.D., M.P.H.

Circulation

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Home > Circulation > Vol. 132, No. 24 > Association of Coffee Consumption With Total and Cause-Specific Mortality in ...

FREE ACCESS RESEARCH ARTICLE

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Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts

Ming Ding, Ambika Satija, Shilpa N. Bhupathiraju, Yang Hu, Qi Sun, Jiali Han, Esther Lopez-Garcia, Walter Willett, Rob M. van Dam and Frank B. Hu

Tools Share

Circulation

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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VOL. 75, NO. 15, 2020

ORIGINAL INVESTIGATIONS

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Home > Circulation > Vol. 143, No. 17 > Fruit and Vegetable Intake and Mortality

FREE ACCESS RESEARCH ARTICLE

Fruit and Vegetable Intake and Mortality

Results From 2 Prospective Cohort Studies of US Men and Women and a Meta-Analysis of 26 Cohort Studies

Dong D. Wang, Yanping Li, Shilpa N. Bhupathiraju, Bernard A. Rosner, Qi Sun, Edward L. Giovannucci, Eric B. Rimm, JoAnn E. Manson, Walter C. Willett, Meir J. Stampfer and Frank B. Hu

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Olive Oil Consumption and Cardiovascular Risk in U.S. Adults

Marta Guasch-Ferré, PhD, Gang Liu, PhD, Yanping Li, PhD, Laura Sampson, RD, JoAnn E. Manson, MD, DrPH, Jordi Salas-Salvadó, MD, PhD, Miguel A. Martínez-González, MD, PhD, Meir J. Stampfer, MD, PhD, Walter C. Willett, MD, DrPH, Qi Sun, MD, PhD, Frank B. Hu, MD, PhD



Circulation

AHA Journals Journal Information All Issues Subjects Features Resource

Home > Circulation > Vol. 133, No. 24 > Whole Grain Intake and Mortality From All Causes, Cardiovascular Disease, an...

FREE ACCESS RESEARCH ARTICLE

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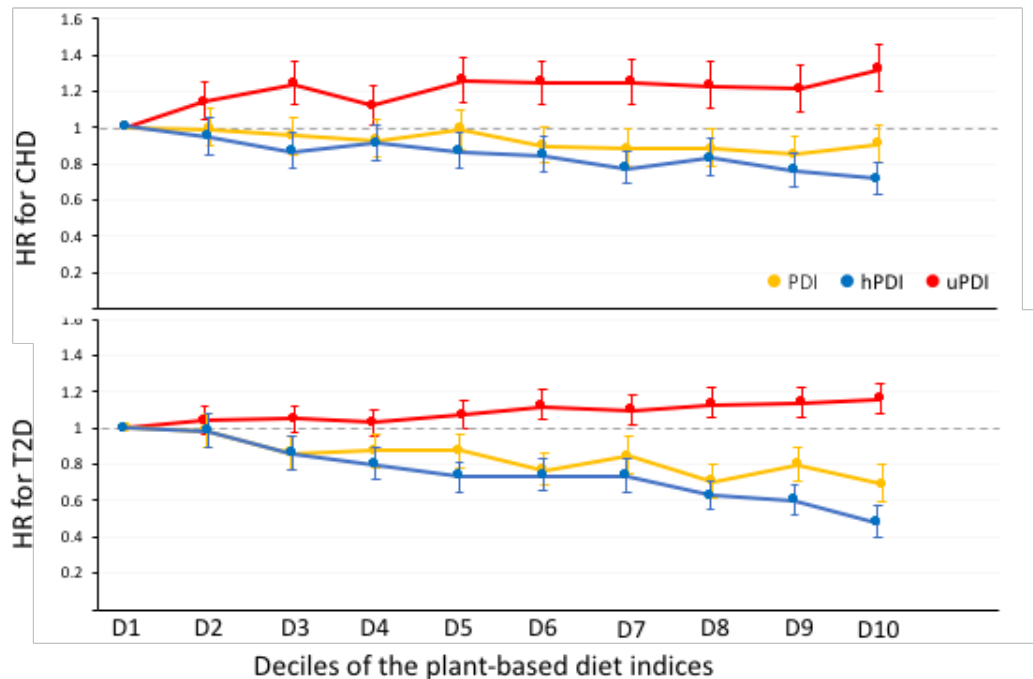
Whole Grain Intake and Mortality From All Causes, Cardiovascular Disease, and Cancer A Meta-Analysis of Prospective Cohort Studies

Geng Zong, Alisa Gao, Frank B. Hu and Qi Sun

Tools Share

Originally published 14 Jun 2016 | https://doi.org/10.1161/CIRCULATIONAHA.115.021101 | Circulation. 2016;133:2370-2380

Not all plant-based diets are healthy



Satija et al, J Am Coll Cardiol 2017
Satija et al. PLoS Medicine 2016

- Healthy plant-based diets rich in whole grains, fruits/vegetables, nuts/legumes, oils, coffee/tea are associated with lower T2D, CVD, and mortality risk
- Unhealthy plant-based diets high in sweetened beverages, refined grains, potatoes/fries, sweets are associated with increased risk of chronic diseases and mortality – worse than animal food-based diets
- These findings underscore the quality of plant foods in our diet



ORIGINAL ARTICLE | FEBRUARY 28 2023

Ultra-Processed Food Consumption and Risk of Type 2 Diabetes: Three Large Prospective U.S. Cohort Studies **FREE**

Zhangling Chen ; Neha Khandpur; Clémence Desjardins; Lu Wang; Carlos A. Monteiro; Sinara L. Rossato; Teresa T. Fung; JoAnn E. Manson; Walter C. Willett; Eric B. Rimm; Frank B. Hu ; Qi Sun ; Jean-Philippe Drouin-Chartier



> *J Natl Cancer Inst.* 2023 Feb 8;115(2):155-164. doi: 10.1093/jnci/djac221.

Ultra-processed food consumption and risk of colorectal cancer precursors: results from 3 prospective cohorts

Dong Hang ^{1 2}, Lu Wang ³, Zhe Fang ⁴, Mengxi Du ³, Kai Wang ^{2 6 7}, Neha Khandpur ^{2 6 7}, Sinara L Rossato ^{6 8}, Kana Wu ², Zhibo Shuji Ogino ^{9 10 11 12}, Andrew T Chan ^{9 12 13}, Edward L Giovannucci ³, Fang Fang Zhang ³, Mingyang Song ^{2 4 13}

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Research

Maternal consumption of ultra-processed foods and subsequent risk of offspring overweight or obesity: results from three prospective cohort studies

BMJ 2022 ; 379 doi: <https://doi.org/10.1136/bmj-2022-071767> (Published 05 October 2022)

Cite this as: *BMJ* 2022;379:e071767

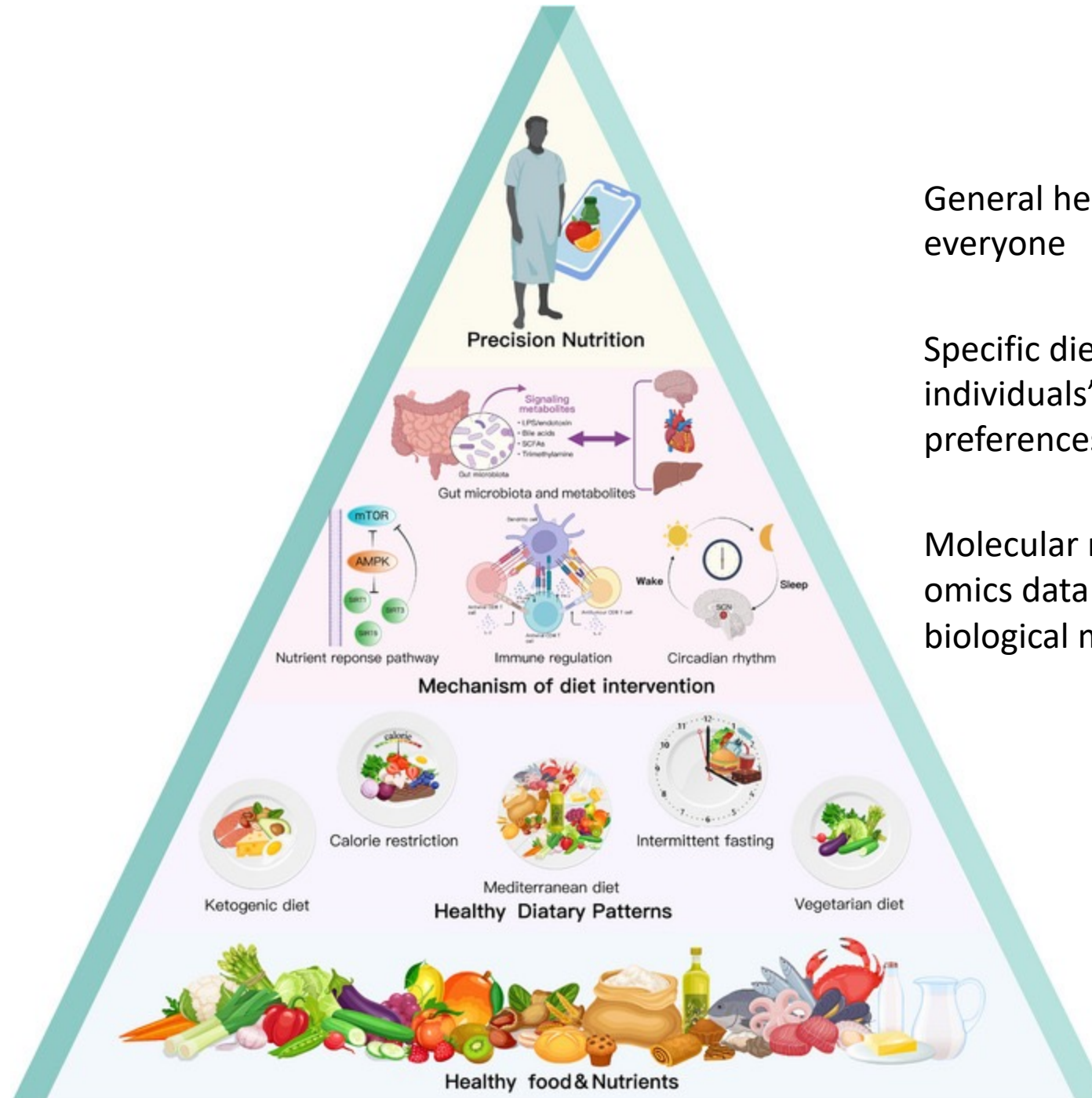
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One size
doesn't fit
all





- “**Precision Nutrition** is a framework canvassing a wide array of features including genetics, dietary habits and eating patterns, circadian rhythms, health status, socioeconomic and psychosocial characteristics, food environments, physical activity, and the microbiome.”
- **Personalized nutrition** or nutrigenomics: Tailor nutritional strategies to individual characteristics such as genetic variants and gut microbiome.
- **Precision Nutrition** recognizes that humans are inherently different from one another, so **when, why,** and **how** we eat is likely as important as **what** we eat.



General healthy diet guidelines for everyone

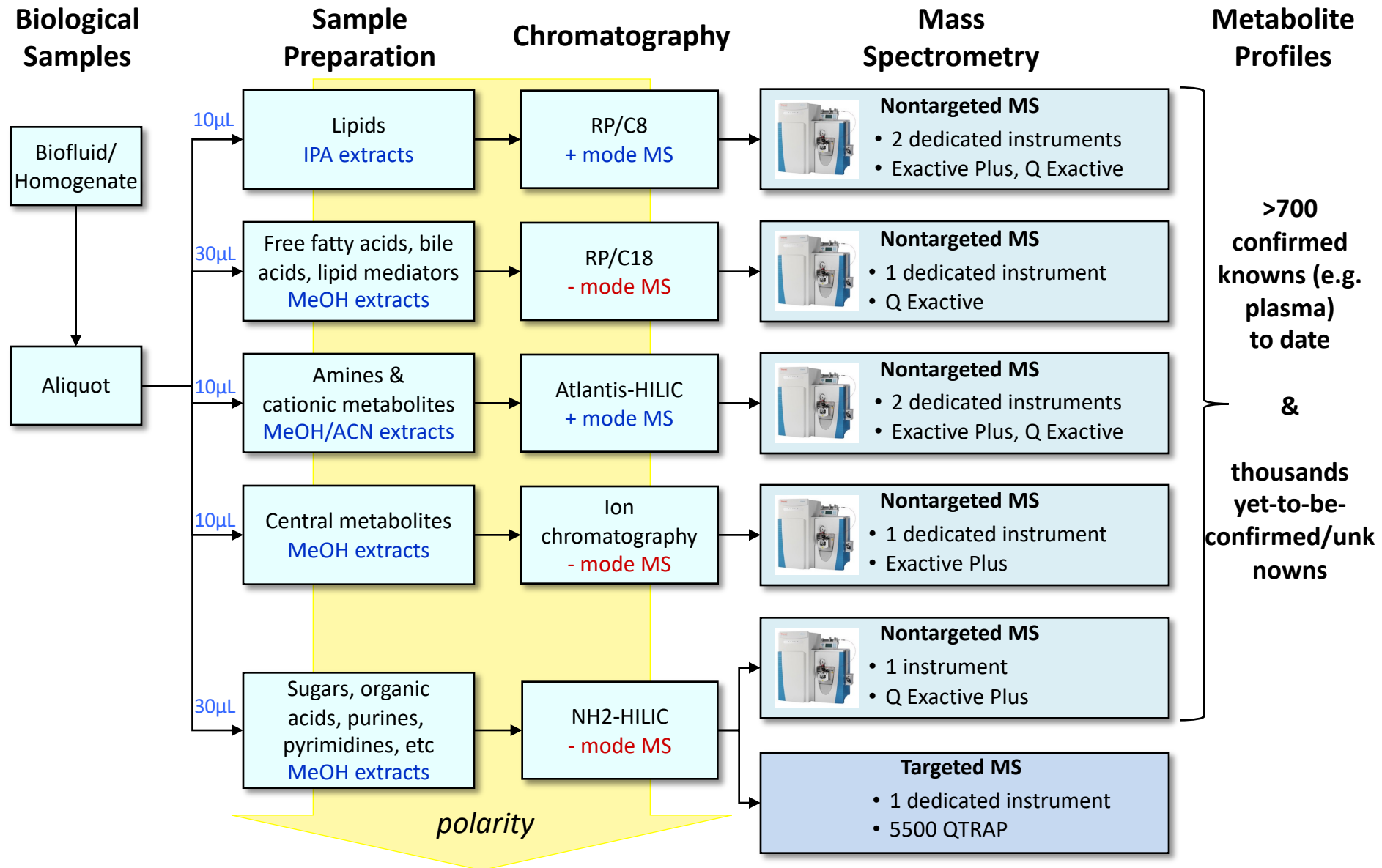


Specific diet recommendations based on individuals' health conditions and food preferences



Molecular nutrition advice based on omics data and our understanding of biological mechanisms

LC-MS-based approach (Clary Clish, Broad)



The role of precision nutrition in research and practice

1

Improve dietary
assessment and
compliance

2

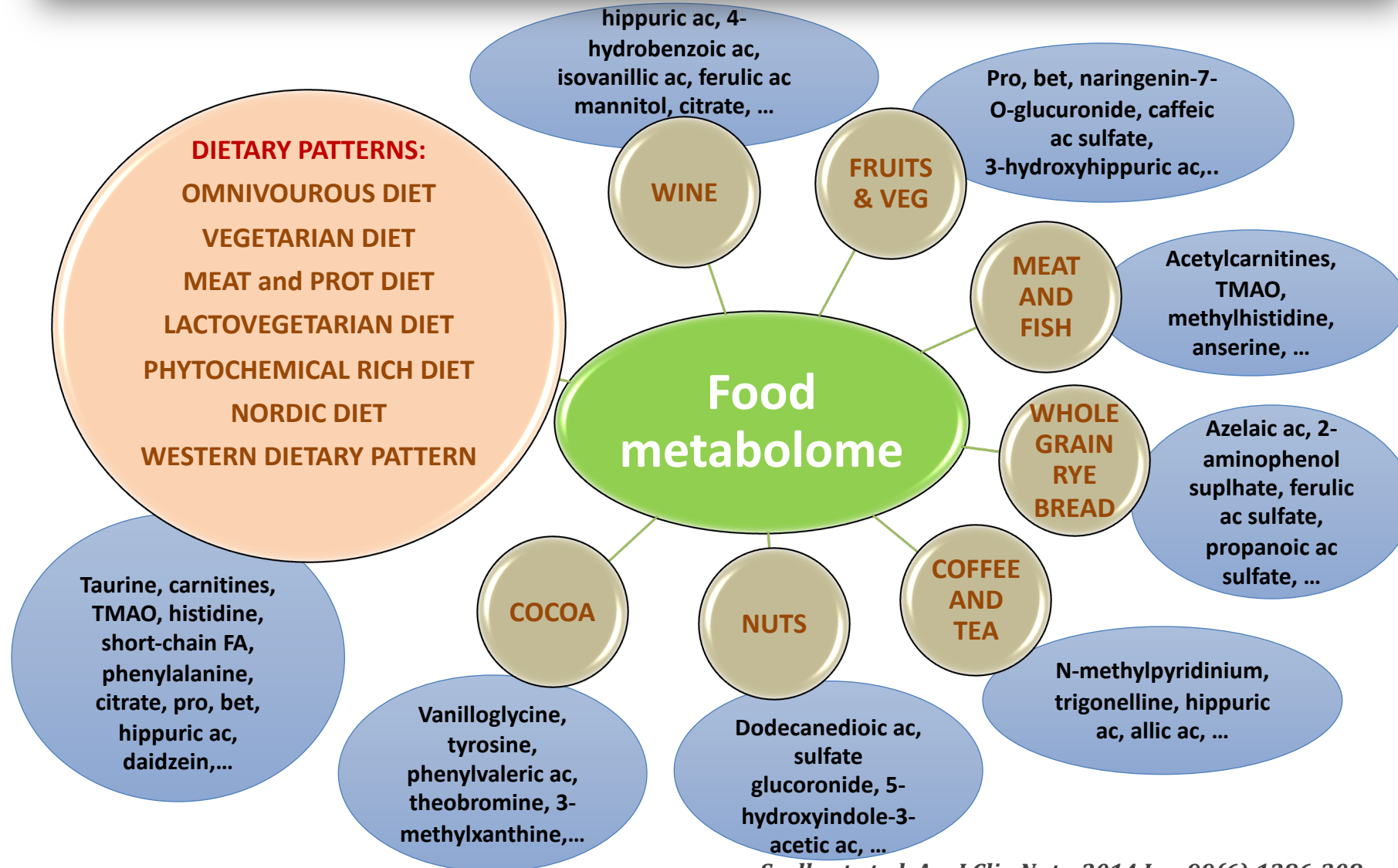
Better understand
biological
mechanisms

3

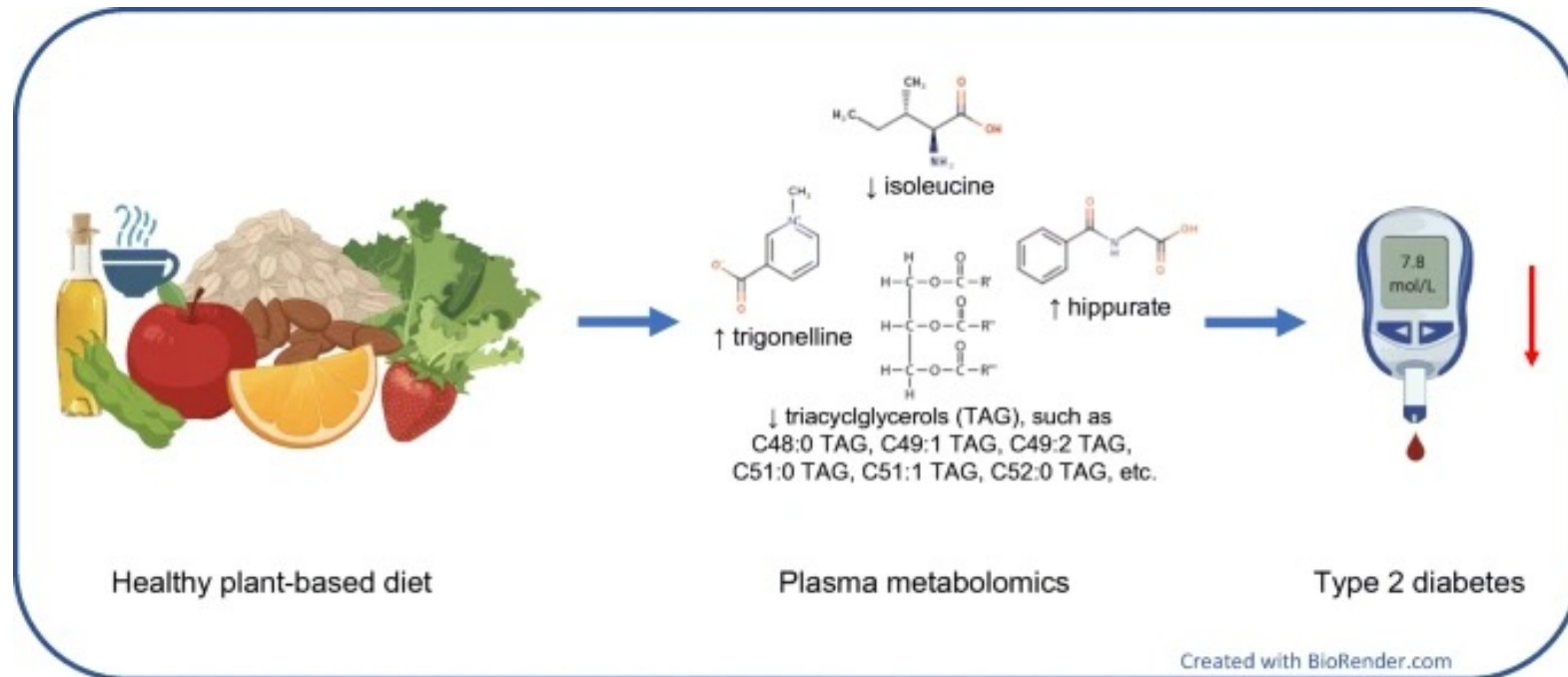
More effective
personalized nutrition
strategies to improve
health outcomes

The food metabolome: a window over dietary exposure¹⁻³

Augustin Scalbert, Lorraine Brennan, Claudine Manach, Cristina Andres-Lacueva, Lars O Dragsted, John Draper, Stephen M Rappaport, Justin JJ van der Hoof, and David S Wishart



Plasma metabolite profiles related to plant-based diets and the risk of type 2 diabetes



- Unique multi-metabolite profiles differed significantly between the healthy and unhealthy plant-based diets.

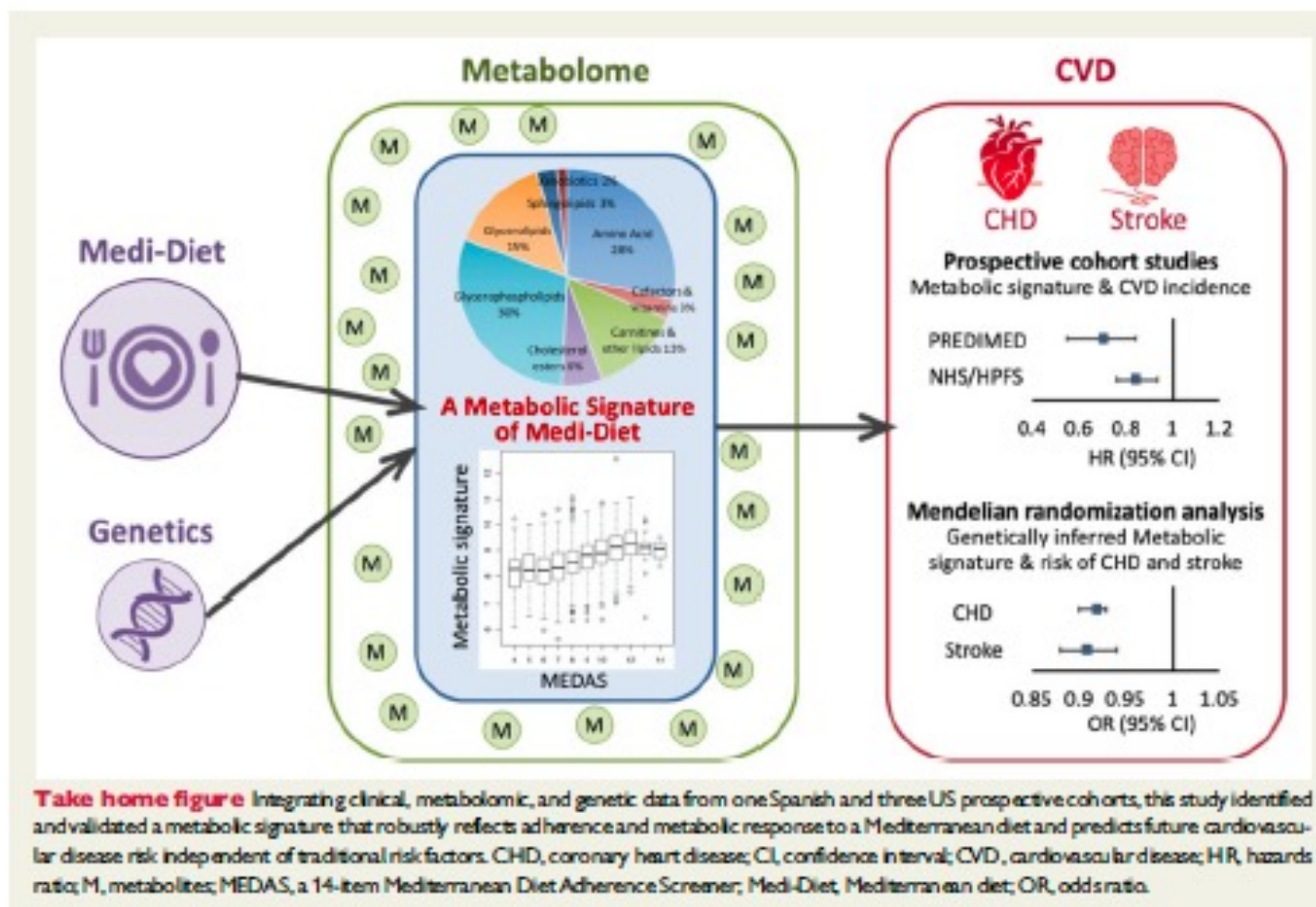
- hPDI is characterized by higher plasma trigonelline and hippurate, low levels of isoleucine and some lipid metabolites.

- Metabolite profile scores for hPDI were inversely associated with incident T2D independent of BMI, and other diabetes risk factors.

- Support the beneficial role of healthy plant-based diets in diabetes prevention and provide new insights into mechanisms

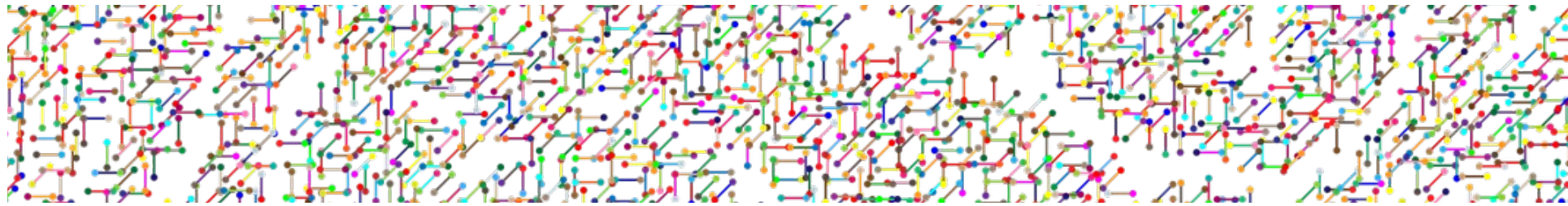
The Mediterranean diet, plasma metabolome, and cardiovascular disease risk

Downloaded



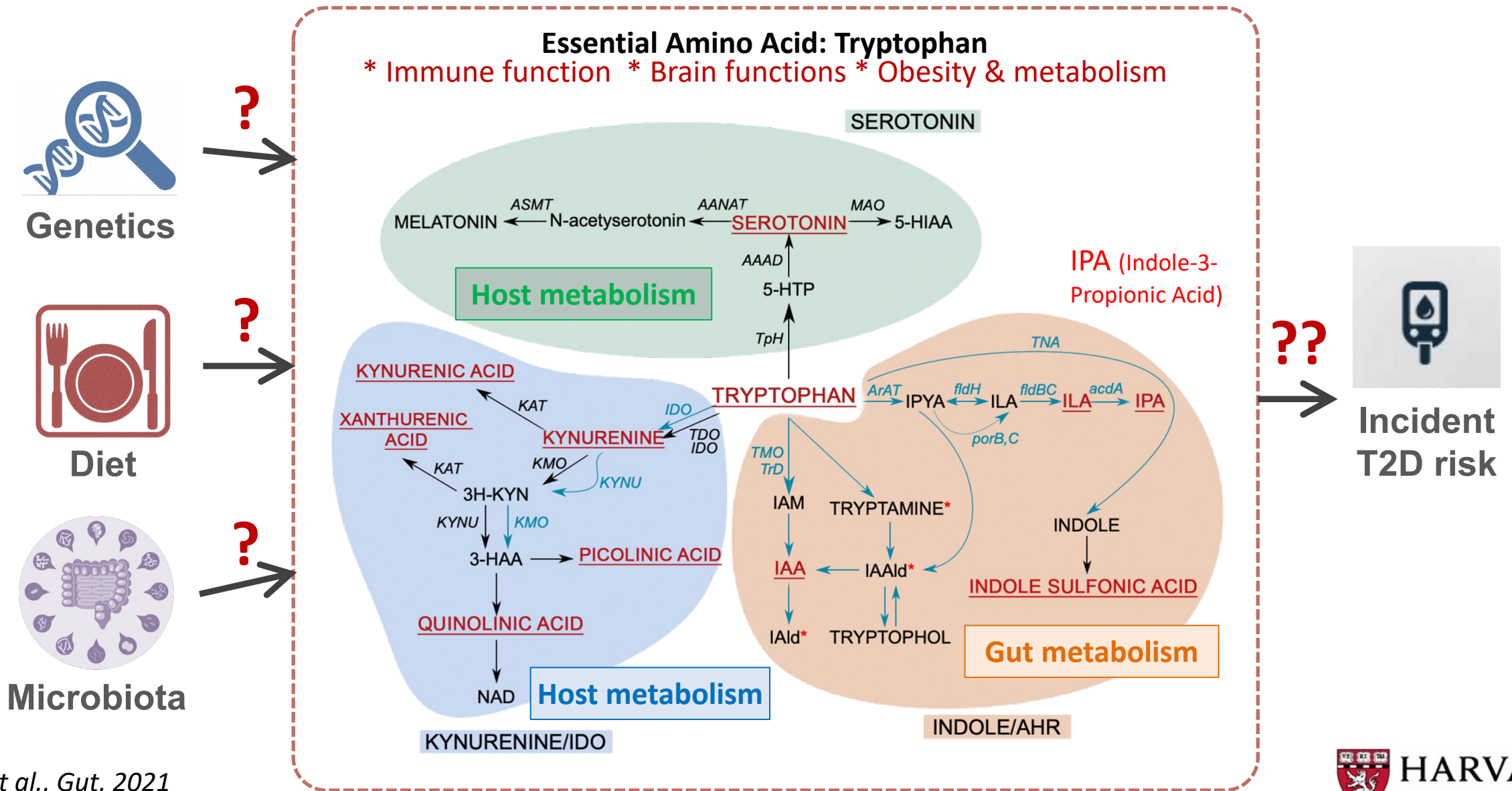
Elucidating Biological Mechanisms

- Multi-omics analysis can help understand:
 - The relationship between diet and disease risk at molecular levels
 - Individuals' variability in response to dietary interventions



INTERPLAY between host and gut microbial metabolism

Tryptophan and risk of type 2 diabetes



Primary study (Discovery) cohort



Hispanic Community Health Study/Study of Latinos (SOL)

- Prospective, 16,415 US Hispanic/Latinos
- Baseline Metabolomics**
 - Metabolon
 - **367 incident T2D in 2,821 healthy participants**
- GWAS: 3,933** overlapping with metabolomics
- Gut microbiome:** shotgun sequencing
- Diet:** 1* FFQ + 2* 24h DDR

Qi Q, et al, Gut, 2021

Replication study cohorts



- Baseline Metabolomics (Metabolon)**
 - **Total n= 2712 healthy participant**
 - **1036 incident T2D**
- GWAS: 3281** overlapping with metabolomics



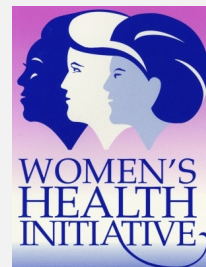
Framingham Heart Study

- Baseline Metabolomics (Broad institute)**
 - **Total n=1424 healthy participant**
 - **218 incident T2D**
- GWAS: 1509** also with metabolomics



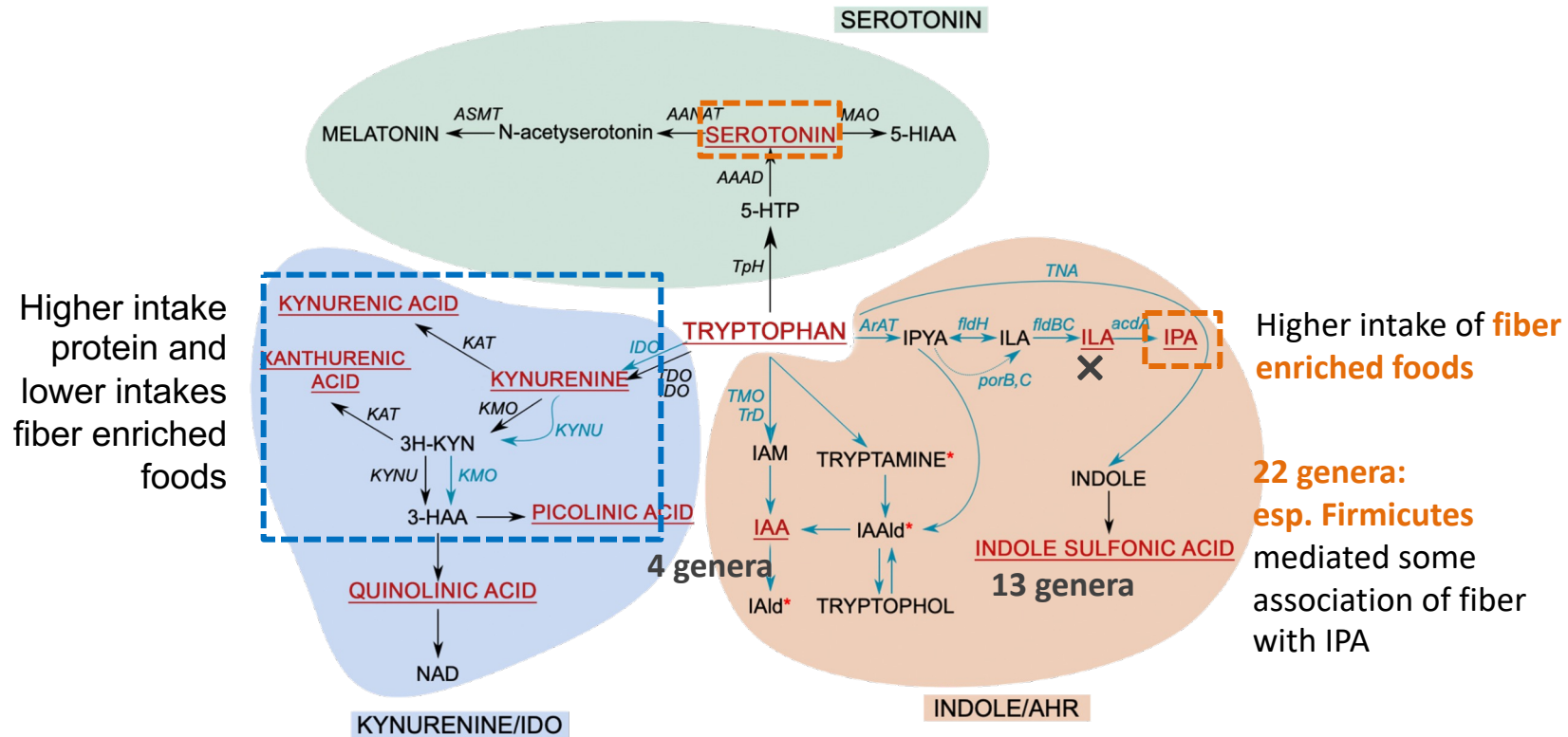
PREDIMED Study

- Baseline Metabolomics (Broad institute)**
 - **694 sub-cohort participants**
 - **251 incident T2D**



- Baseline Metabolomics (Broad institute)**
 - **Total n=1392 healthy participant**
 - **163 incident T2D**

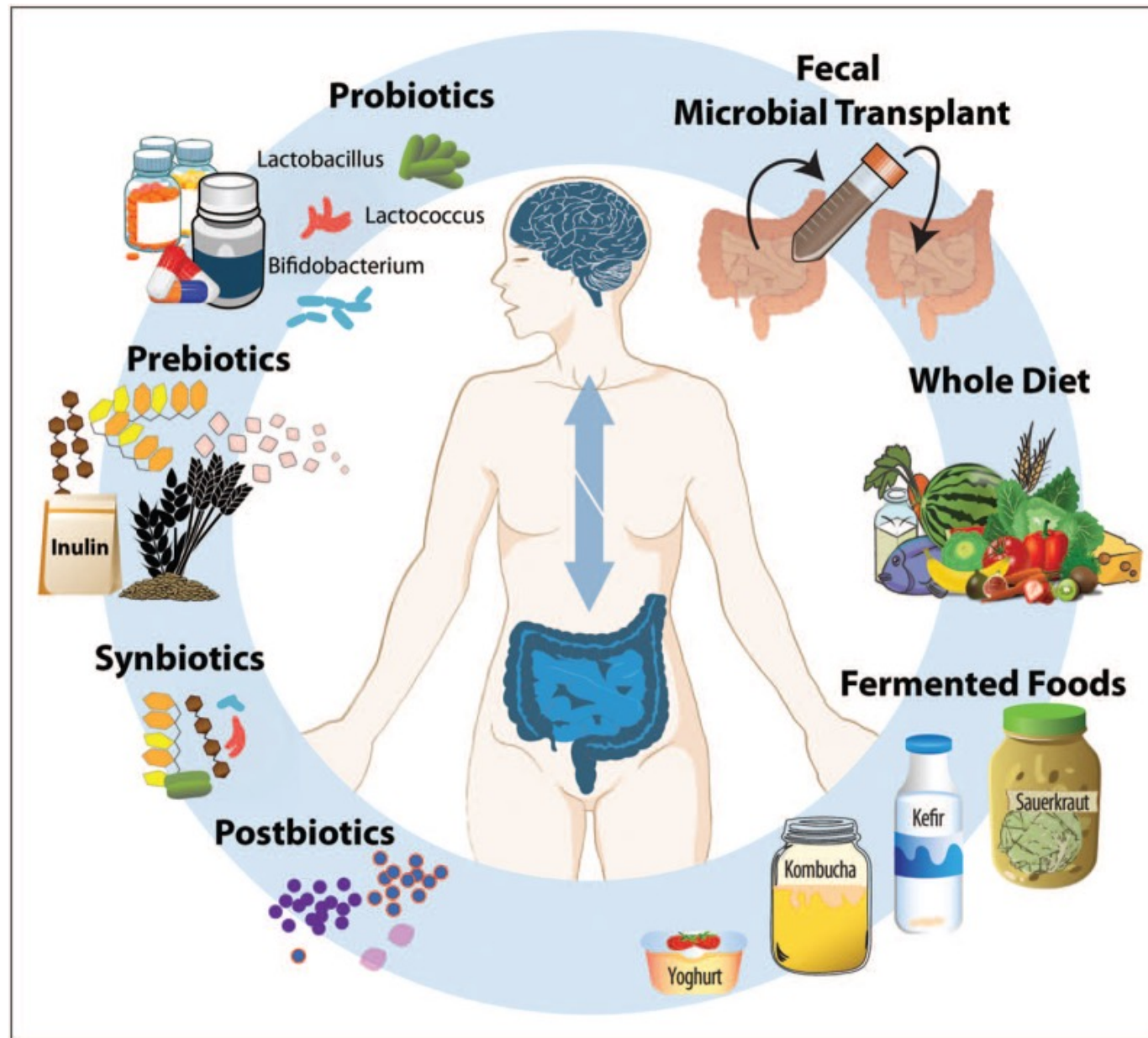
Host and gut microbial tryptophan metabolism and T2D



● Host tryptophan and its kynurenine-related pathway metabolites showed positive associations with T2D, while microbial pathway metabolite IPA (Indole-3-propionic acid) showed inverse association.

● Plant-based fiber-rich diets were associated increased IPA and a diet in high in animal protein was associated with increased kynurenine metabolites

● The effects of fiber-rich diets on beneficial metabolites are partly mediated through gut microbiome composition (shift from host metabolic pathways to microbial pathways)



Microbiota-targeted interventions

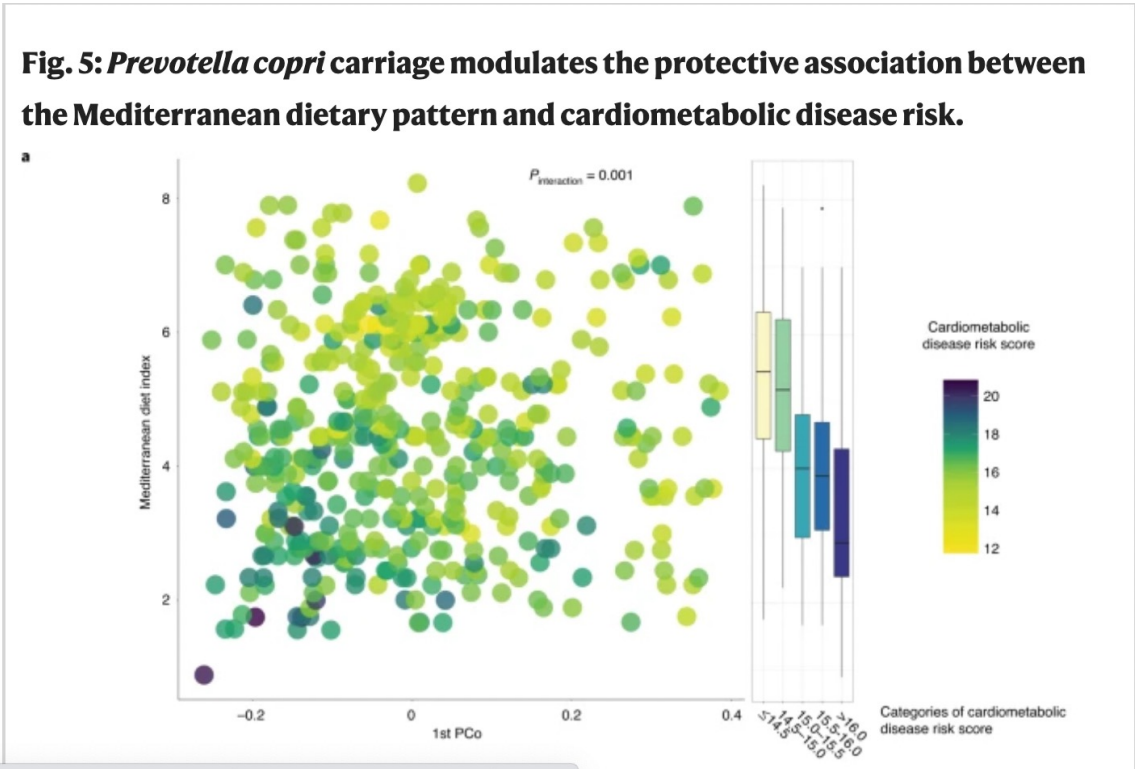
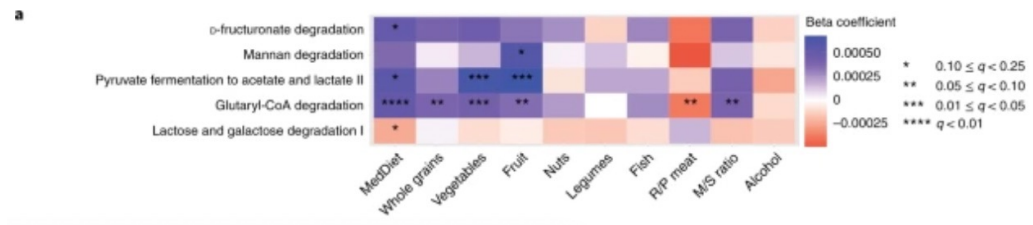
Article | Published: 11 February 2021

The gut microbiome modulates the protective association between a Mediterranean diet and cardiometabolic disease risk

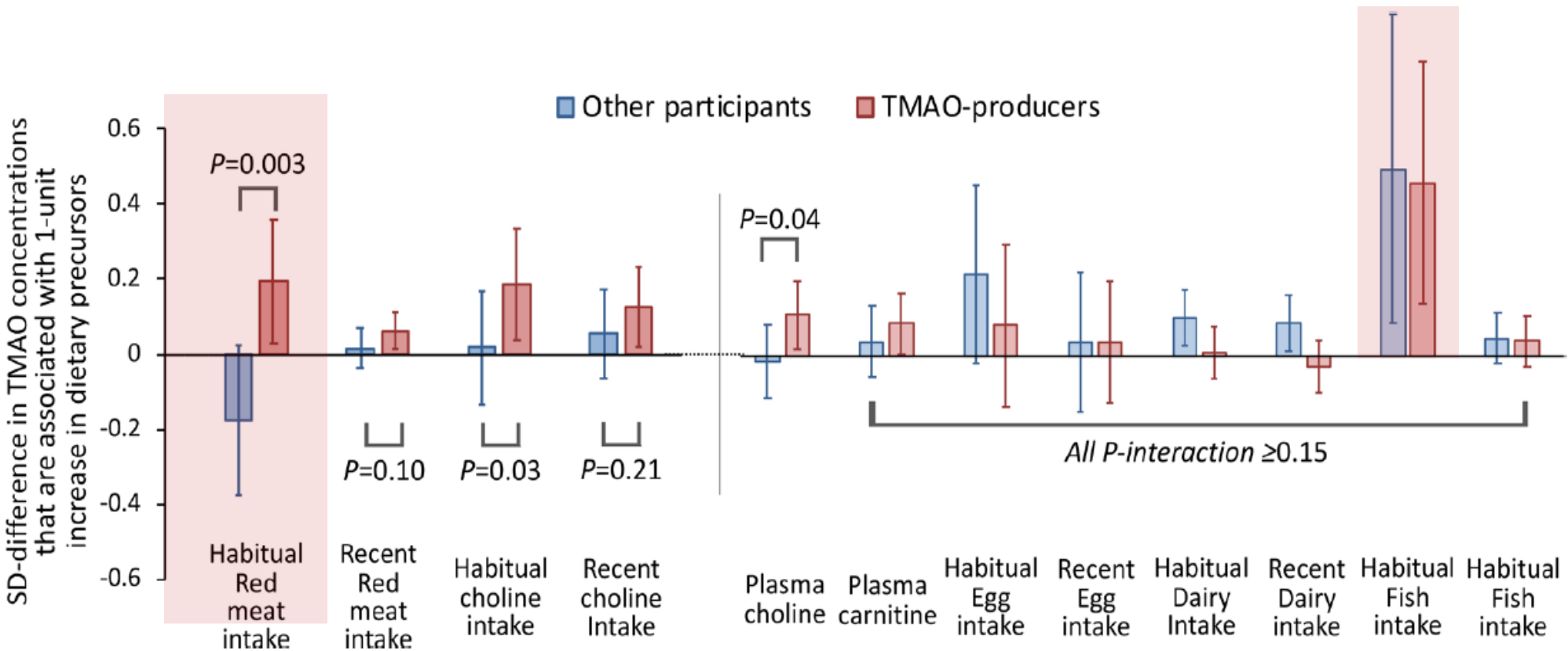
Dong D. Wang, Long H. Nguyen, Yanping Li, Yan Yan, Wenjie Ma, Ehud Rinott, Kerry L. Ivey, Iris Shai, Walter C. Willett, Frank B. Hu, Eric B. Rimm, Meir J. Stampfer, Andrew T. Chan & Curtis Huttenhower ✉

Nature Medicine 27, 333–343 (2021) | Cite this article

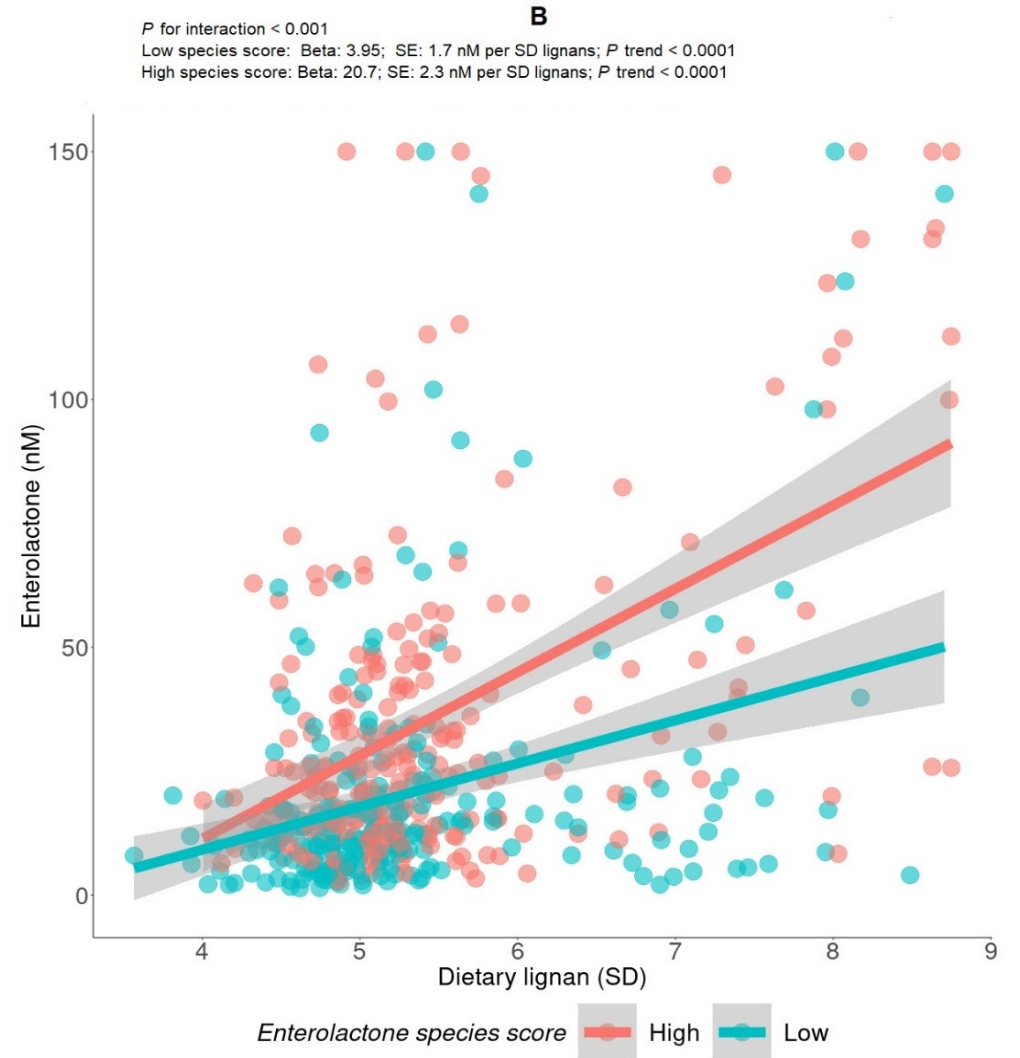
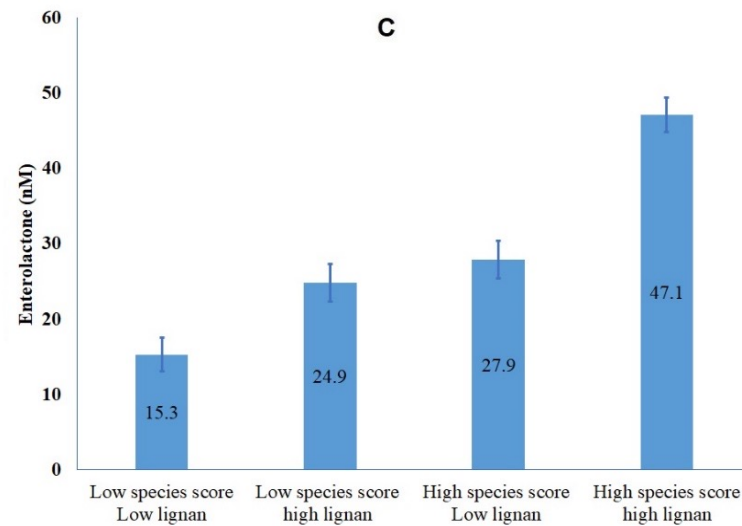
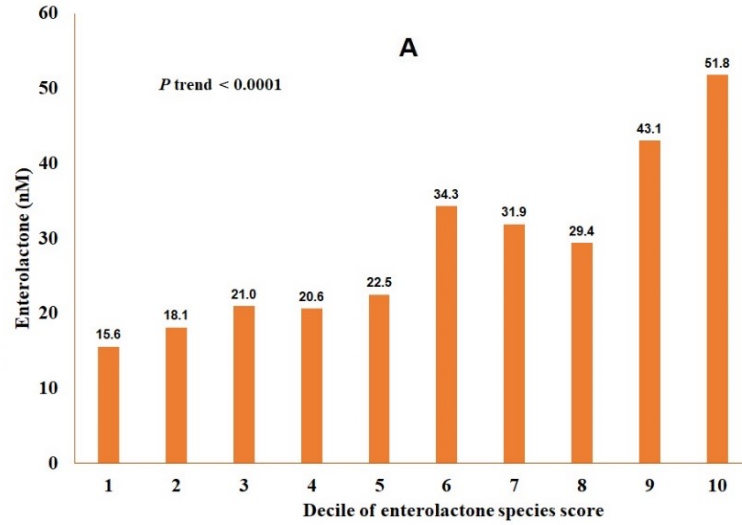
Fig. 4: The Mediterranean dietary pattern is associated with microbial processes involved in plant polysaccharide degradation and short-chain fatty acid production.



Diet and gut microbiome interaction and TMAO



Lignans, Microbiome, and Enterolactone

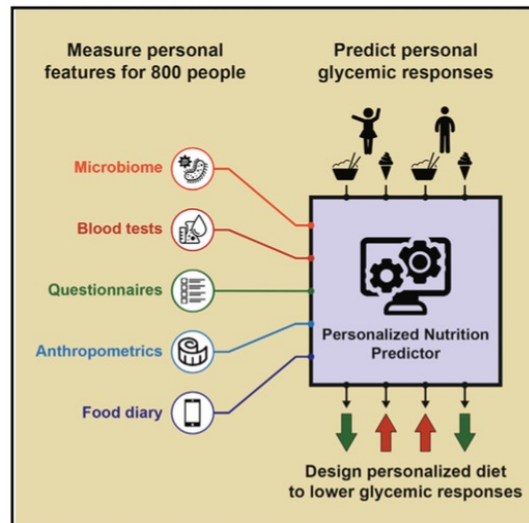


Personalized Nutrition based on Computer Algorithms

Cell

Personalized Nutrition by Prediction of Glycemic Responses

Graphical Abstract



Zeevi et al. Cell. Nov 2015

Authors

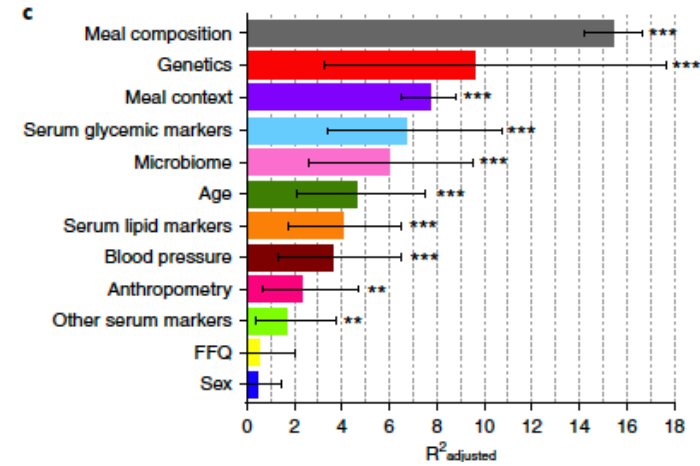
David Zeevi, Tal Korem, Niv Zmora, ..., Zamir Halpern, Eran Elinav, Eran Segal

Correspondence

eran.elinav@weizmann.ac.il (E.E.), eran.segal@weizmann.ac.il (E.S.)

In Brief

People eating identical meals present high variability in post-meal blood glucose response. Personalized diets created with the help of an accurate predictor of blood glucose response that integrates parameters such as dietary habits, physical activity, and microbiota may successfully meal blood glucose and its metabolic consequences.



Human postprandial responses to food and potential for precision nutrition

Sarah E. Berry^{1,15}, Ana M. Valdes^{2,3,15} ✉, David A. Drew⁴, Francesco Asnicar⁵, Mohsen Mazidi⁶, Jonathan Wolf⁷, Joan Capdevila⁷, George Hadjigeorgiou⁷, Richard Davies⁷, Haya Al Khatib^{1,7}, Christopher Bonnett⁷, Sajaysurya Ganesh⁷, Elco Bakker⁷, Deborah Hart⁶, Massimo Mangino⁶, Jordi Merino^{4,8,9}, Inbar Linenberg⁷, Patrick Wyatt⁷, Jose M. Ordovas^{10,11}, Christopher D. Gardner¹², Linda M. Delahanty⁴, Andrew T. Chan⁴, Nicola Segata¹⁵, Paul W. Franks^{6,13,14,15} and Tim D. Spector^{6,15} ✉

The role of precision nutrition in research and practice

Dietary assessment

- Holds promises for novel biomarker discovery for food intakes and dietary patterns
- Complementary to rather than a replacement for traditional nutrition biomarkers and self-reported dietary assessment tools

Biological mechanisms

- Most fruitful areas of research
- Black-box epi to Systems epi
- Although new mechanisms may be discovered, clinical translations are challenging and take time

Personalized nutrition advice

- AI-based tools are at early stage; not ready for prime time
- Commercial products outpace the evidence
- More useful for disease management than for prevention
- May widen health disparities

HEALTHY EATING PLATE

HEALTHY OILS
Use healthy oils (like olive and canola oil) for cooking, on salad, and at the table. Limit butter. Avoid trans fat.

WATER
Drink water, tea, or coffee (with little or no sugar). Limit milk/dairy (1-2 servings/day) and juice (1 small glass/day). Avoid sugary drinks.

VEGETABLES
The more veggies – and the greater the variety – the better. Potatoes and French fries don't count.

WHOLE GRAINS
Eat a variety of whole grains (like whole-wheat bread, whole-grain pasta, and brown rice). Limit refined grains (like white rice and white bread).

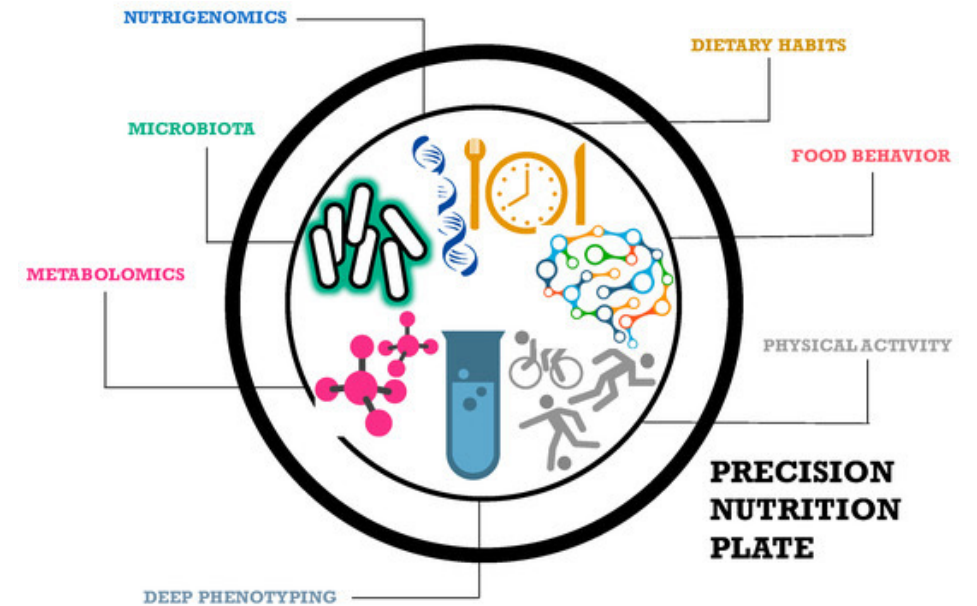
FRUITS
Eat plenty of fruits of all colors.

HEALTHY PROTEIN
Choose fish, poultry, beans, and nuts; limit red meat and cheese; avoid bacon, cold cuts, and other processed meats.

STAY ACTIVE!
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The balance between public health nutrition and precision nutrition

Impact of Nutrition Epidemiology on Dietary Guidelines and Nutrition Policies

- Put more emphasis on types of fat and remove the 30% upper limit on total fat
- Recommend replacing unhealthy fats with healthy fats rather than carbohydrates
- Trans fat labeling and ban by the FDA and global trans fat reduction efforts
- Nutrition facts labeling on added sugar, soda tax
- Focus on healthy eating patterns

Is a healthy diet
for humans also
beneficial for
the health of
the planet?



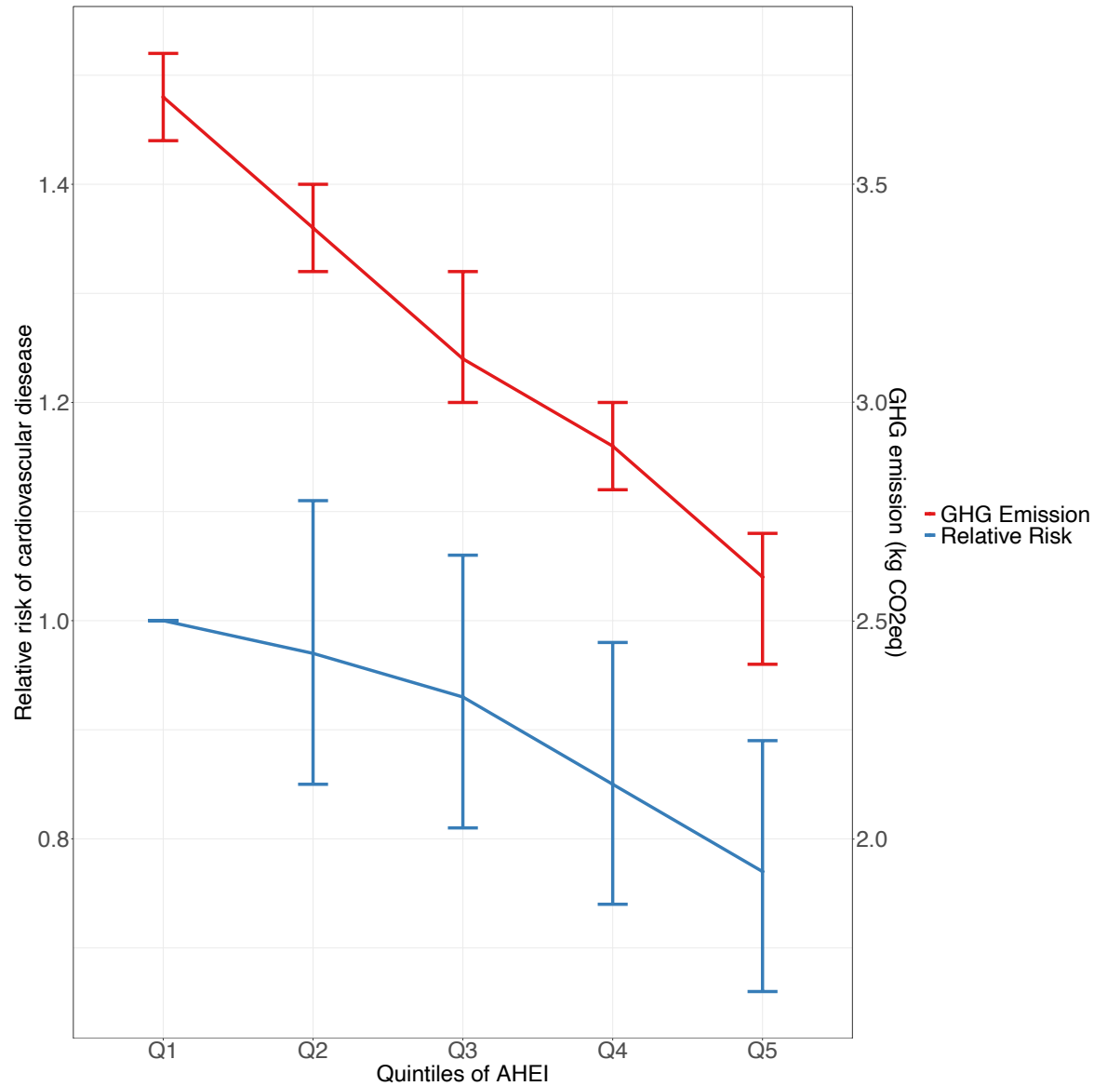
Health and environmental impacts of plant-rich dietary patterns: A U.S. prospective cohort study

↑ Higher score, Higher intake:

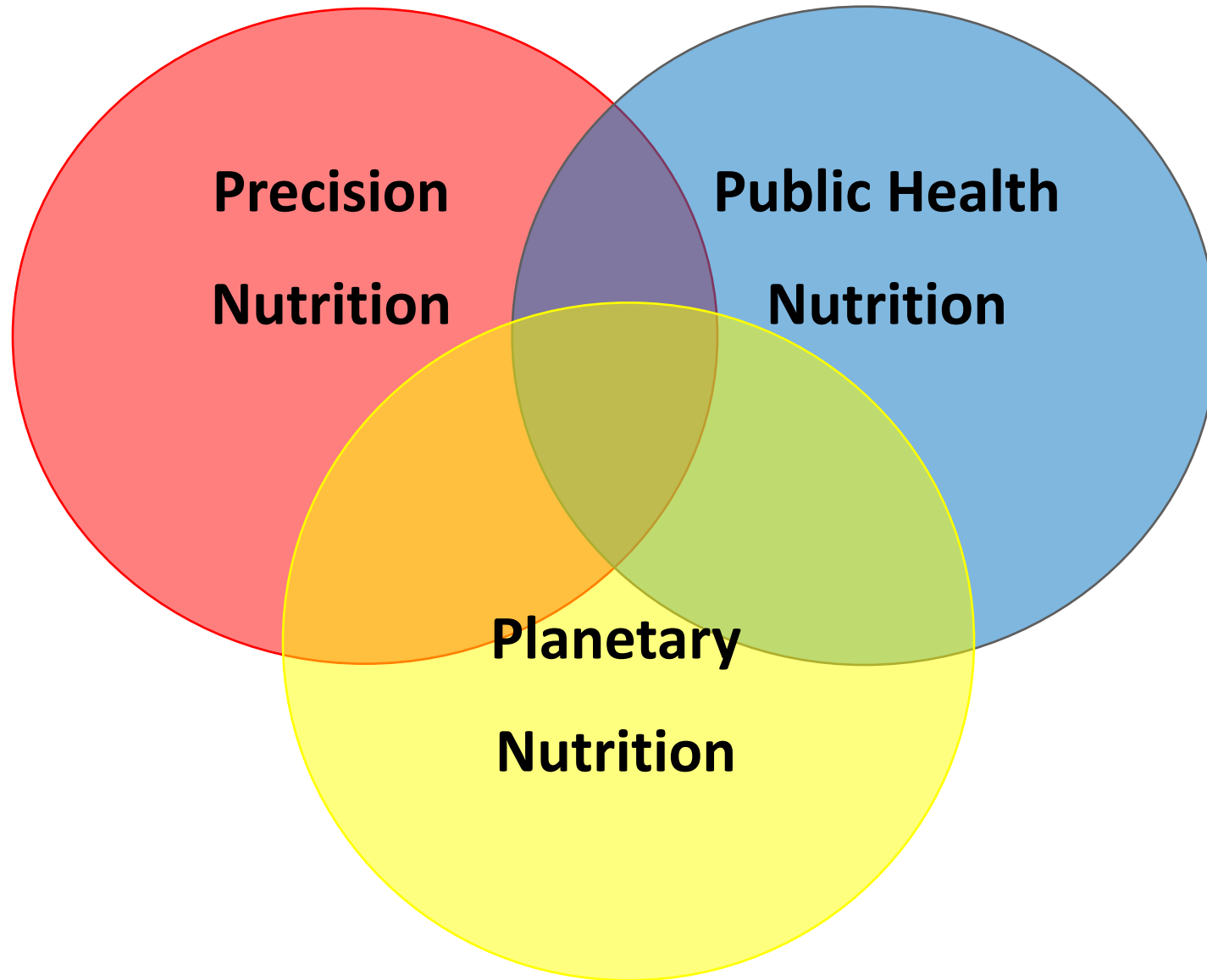
- Vegetables (excl. potatoes & juices)
- Fruits (excl. juices)
- Whole grains
- Nuts and legumes
- ω-3 fats (EPA + DHA)
- Polyunsaturated fat (PUFA)
- Alcohol: J-shape scoring, moderate drinkers have the highest score

↓ Higher score, Lower intake:

- SSBs and juices
- Red/processed meat
- trans fat
- Sodium



An Integrated Approach to Improve Personal, Population, and Planetary Health



Acknowledgements



Nurses'
Health Study

HARVARD
T.H. CHAN
SCHOOL OF PUBLIC HEALTH

HEALTH PROFESSIONALS
FOLLOW-UP STUDY



Predimed
Prevención con Dieta Mediterránea

