Microbiome Revisited

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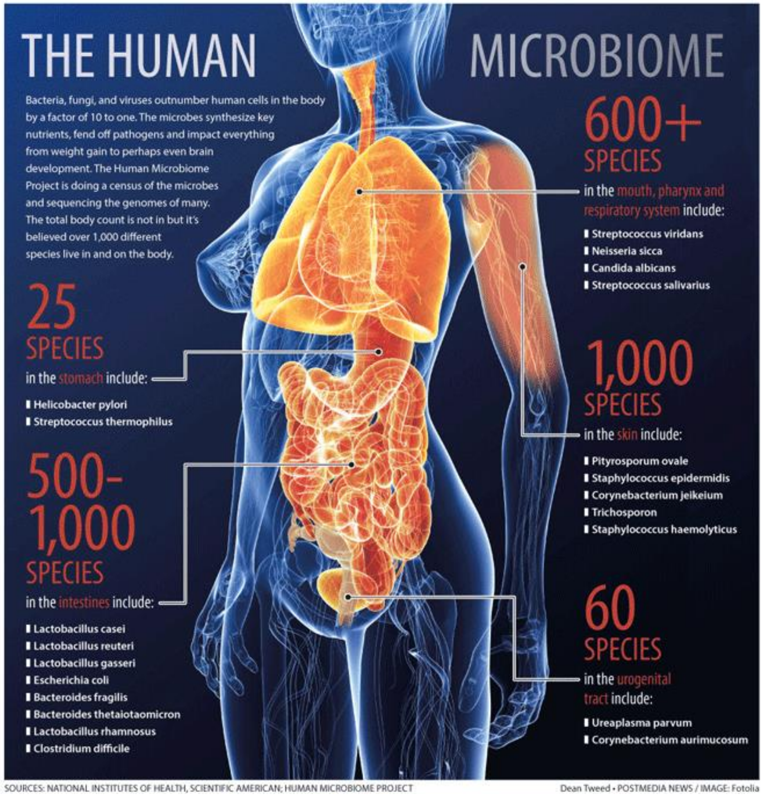
About Myself ..

- Computational Microbiologist
- Human Microbiome
- Data-driven investigation



- Diet - Microbiome
- Life-style Diseases & Aging - Microbiome
- Population-specific Keystone Microbiota
- Cross Body-site Microbiota Interaction

→ **Public + In-house Data**

→ Meta-Analyses
→ Statistical Learning
→ Machine Learning
→ AI / Deep Learning

The human gut microbiome by numbers

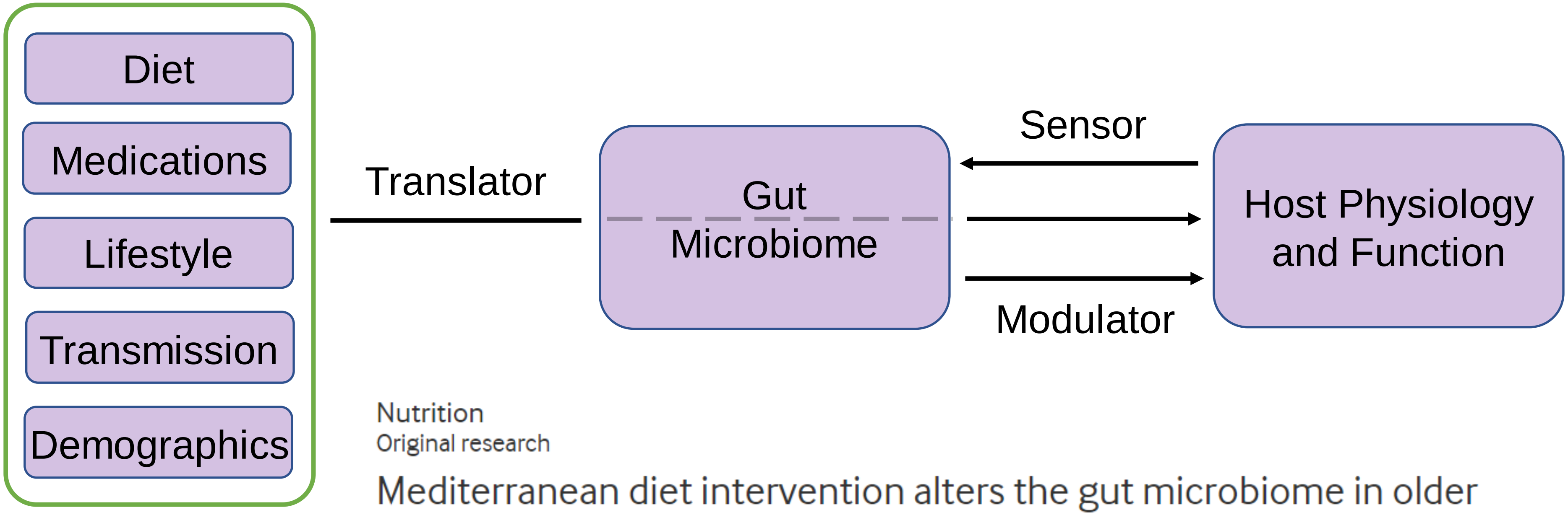
$10^{13} – 10^{14}$
microbial cells

90% of the diseases associated with changes in the gut microbiome

Functional diversity of the microbiome to the human genome:
150 : 1

Microbiome can be therapeutically modifiable

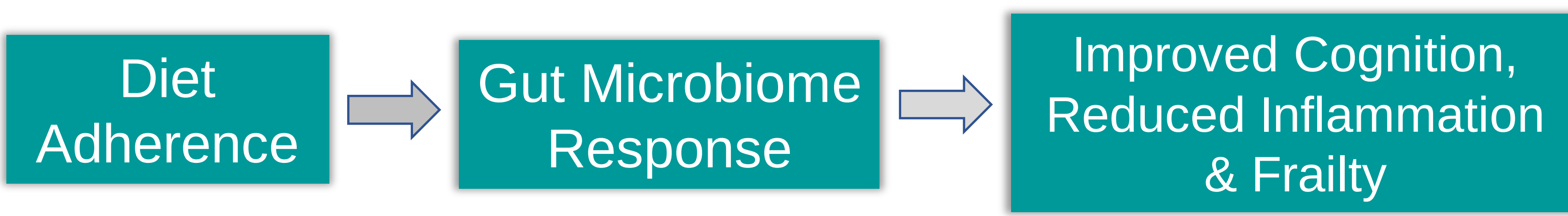
The three facets of the gut microbiome



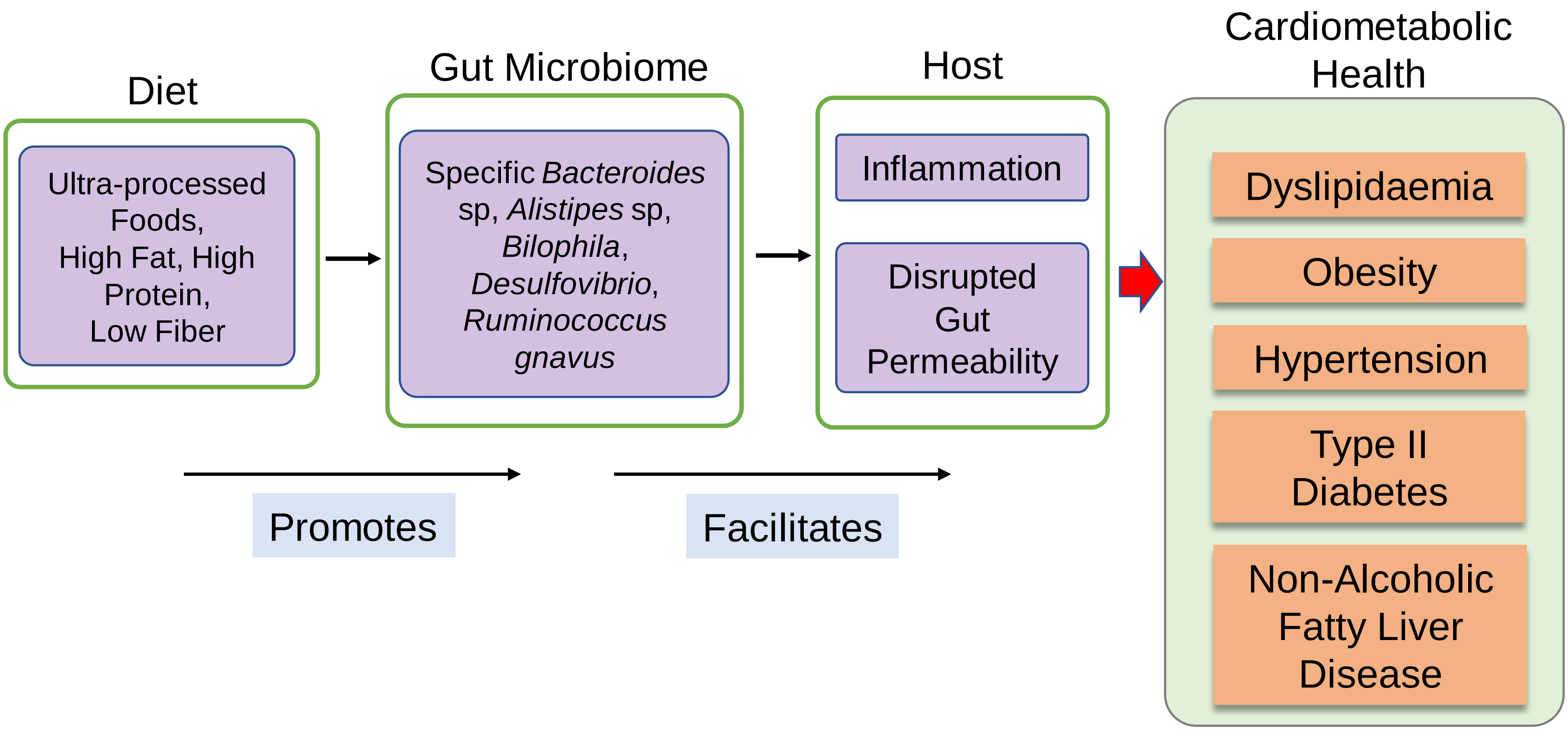
Nutrition
Original research

Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries

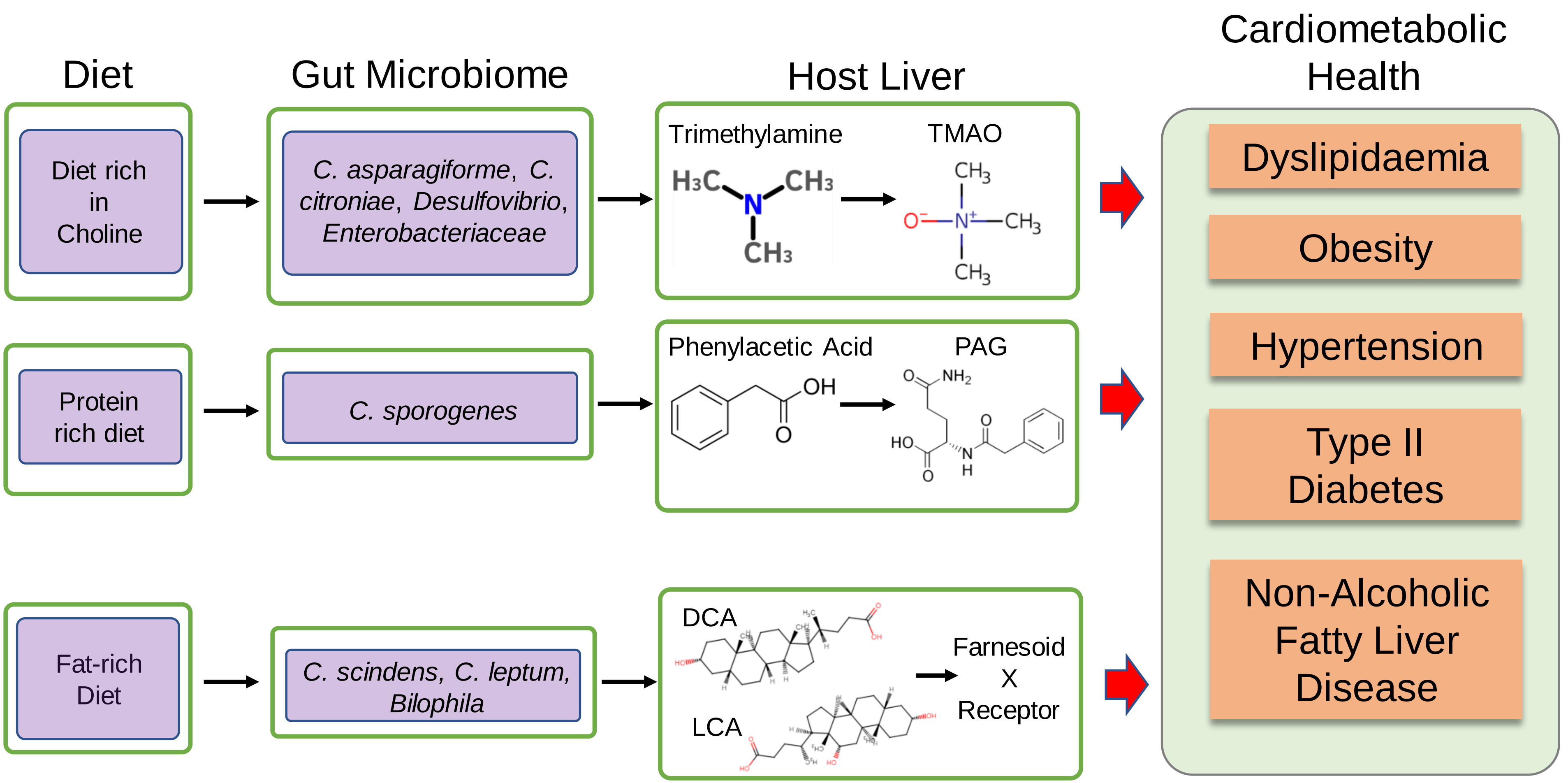
Tarini Shankar Ghosh [1, 2], Simone Rampelli [3], Ian B Jeffery [1, 2], Aurelia Santoro [4, 5], Marta Neto [1, 2], Miriam Capri [3], Enrico Giampieri [4], Amy Jennings [6], Marco Candela [3], Silvia Turroni [3], Erwin G Zoetendal [7], Gerben D A Hermes [7], Caumon Elodie [8], Nathalie Meunier [8], Corinne Malpuech Brugere [9], Estelle Pujos-Guillot [10], Agnes M Berendsen [11], Lisette C P G M De Groot [11], Edith J M Feskins [11], Joanna Kaluza [12], Barbara Pietruszka [12], Marta Jeruszka Bielak [12], Blandine Comte [10], Monica Maijo-Ferre [13], Claudio Nicoletti [13, 14], Willem M De Vos [7, 15], Susan Fairweather-Tait [16], Aedin Cassidy [17], Patrizia



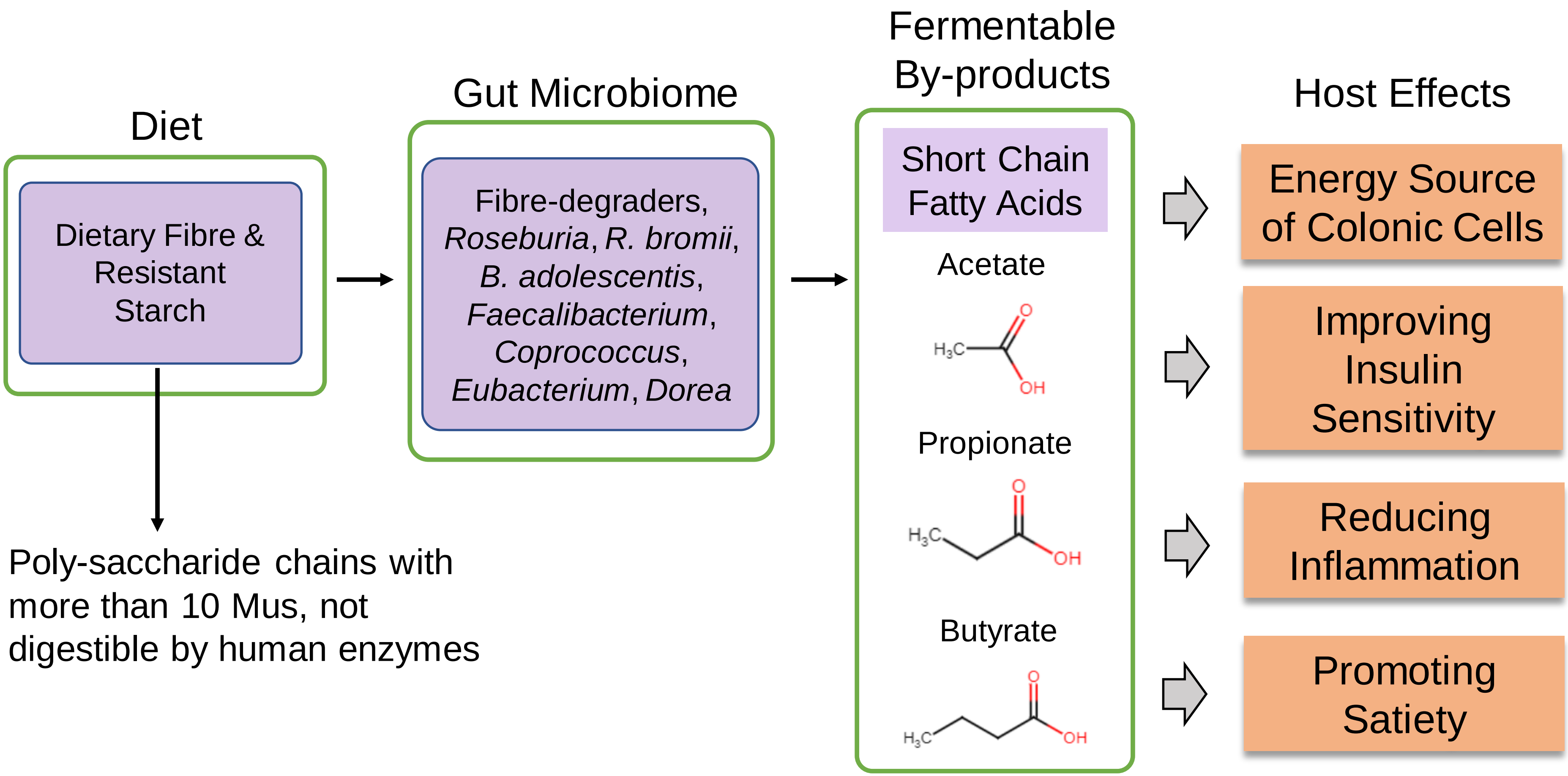
Some examples of detrimental effects of bad diet on gut microbiome on cardiometabolic health



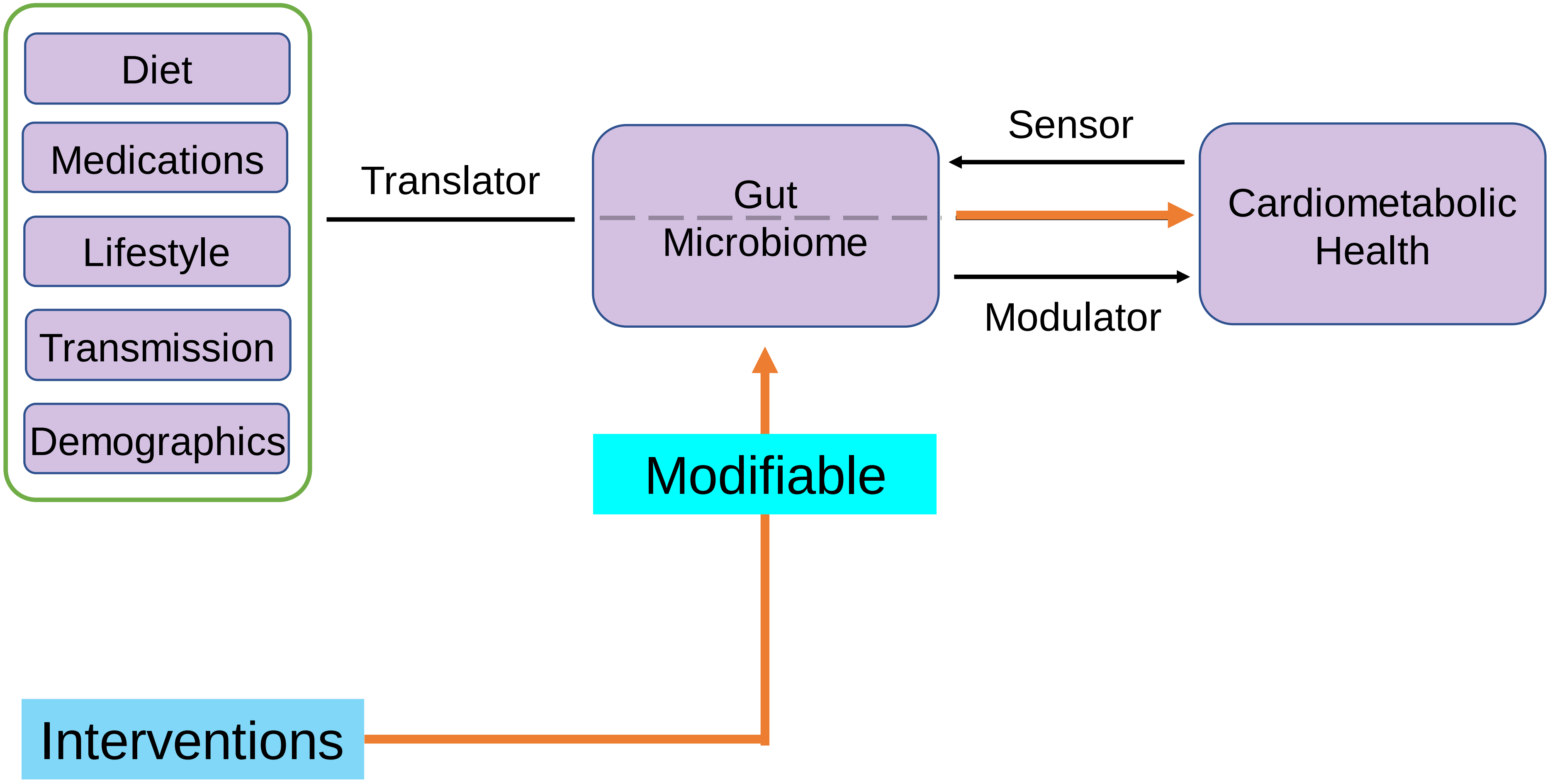
Gut microbiota as a detrimental modulator/translator of cardiometabolic health



Fibre and Short Chain Fatty Acids



Microbiome modifiable using interventions



Microbiome associated interventions

Prebiotics: Substrates that are specifically utilized by ‘beneficial’ host microbes to promote health: beta-Glucan, Fructans, Inulin, Lactulose

Dietary Interventions: Mediterranean Diet, Increased Fibre Intake, Fruits and Vegetables Intake, Reduced Processed Foods

Combinatorial therapies: Dietary Supplementations (Diet + Pro/Pre-biotic)

Probiotics: Live organisms in viable forms that are thought to promote host health, either directly or through cross-feeding: Lactobacilli, Bifidobacteria, etc

Fecal microbiome transplantation: Transfer of fecal matter from a healthy donor to the GI tract of a patient

Synbiotics: Combination of probiotics and prebiotics

Postbiotics: Preparations of inanimate organisms or their components

Lack of consistencies across studies poses challenges: An example of fibre supplementation

- Only 38% of the studies reported a significant link between dietary fibre and SCFAs

nutrients MDPI

Systematic Review

Effects of Dietary Fibers on Short-Chain Fatty Acids and Gut Microbiota Composition in Healthy Adults: A Systematic Review

Valentina Vinelli [1], Paola Biscotti [1], Daniela Martini [1], Cristian Del Bo' [1], Mirko Marino [1], Tomás Meroño [2,3], Olga Nikoloudaki [4], Francesco Maria Calabrese [5], Silvia Turroni [6], Valentina Taverniti [1], Andrea Unión Caballero [2], Cristina Andrés-Lacueva [2,3], Marisa Porrini [1], Marco Gobbetti [4], Maria De Angelis [5], Patrizia Brigidi [7], Mariona Pinart [8], Katharina Nimptsch [8], Simone Guglielmetti [1] and Patrizia Riso [1,*]

- Dependent on dose and fibre structure

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INFLAMMATORY BOWEL DISEASE

- Sometimes the effect can be negative if the modulatory bacteria are absent

Unfermented β-fructan Fibers Fuel Inflammation in Select Inflammatory Bowel Disease Patients

Heather K. Armstrong,[1,2,3] Michael Bording-Jorgensen,[1,2] Deanna M. Santer,[4] Zhengxiao Zhang,[1,5,6] Rosica Valcheva,[1,5] Aja M. Rieger,[7] Justin Sung-Ho Kim,[8,9] Stephanie I. Dijk,[1,10] Ramsha Mahmood,[3] Olamide Ogungbola,[4] Juan Jovel,[1] France Moreau,[11] Hayley Gorman,[11] Robyn Dickner,[1,2] Jeremy Jerasi,[1,2] Inderdeep K. Mander,[1,2] Dawson Lafleur,[1,2] Christopher Cheng,[1,2] Alexandra Petrova,[2] Terri-Lyn Jeanson,[3] Andrew Mason,[1,5] Consolato M. Sergi,[12] Arie Levine,[13] Kris Chadee,[11] David Armstrong,[8] Sarah Rauscher,[8,9,14] Charles N. Bernstein,[3] Matthew W. Carroll,[2] Hien Q. Huynh,[2] Jens Walter,[1,15] Karen L. Madsen,[1,5] Levinus A. Dieleman,[1,5] and Eytan Wine[1,2,10]

There is to survey the evidence for clinical interventions targeting the gut microbiome in cardiometabolic disease

The premise of the current study

214 human clinical intervention studies targeting the gut microbiome and cardiometabolic diseases

- Location of the trials
- Demographics
- Cohort Size
- Duration

Different Intervention Types

- Diet
- Probiotic
- Prebiotic
- Synbiotics
- Diet + Others

Clinical Targets

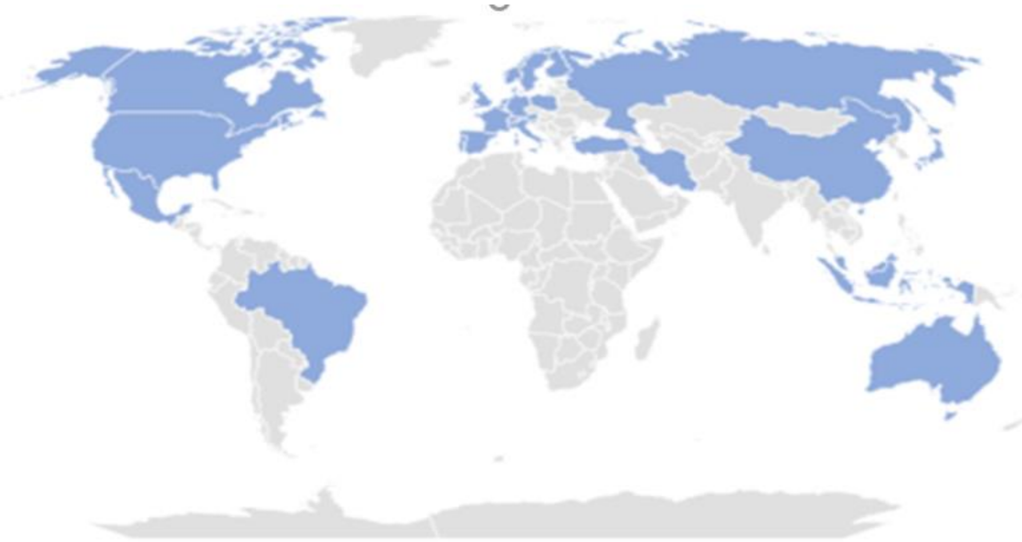
- Obesity
- Cardiovascular Disease
- T2D/Insulin Resistance/GDM
- Metabolic Syndrome & General CMD Risk
- NAFLD & Variants

Intervention Efficacy

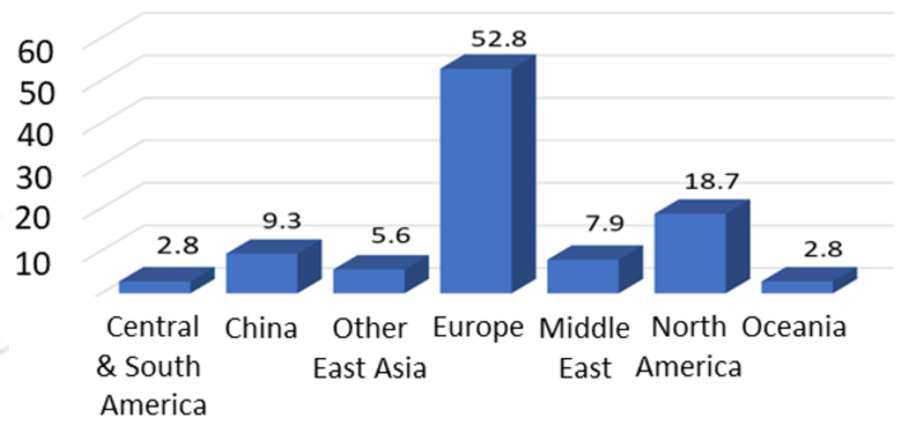
- Host Effect
- Microbiome Effect
- Microbiome Mediated Effect

Large-scale geographical trials in trial locations

Countries where trials have been performed

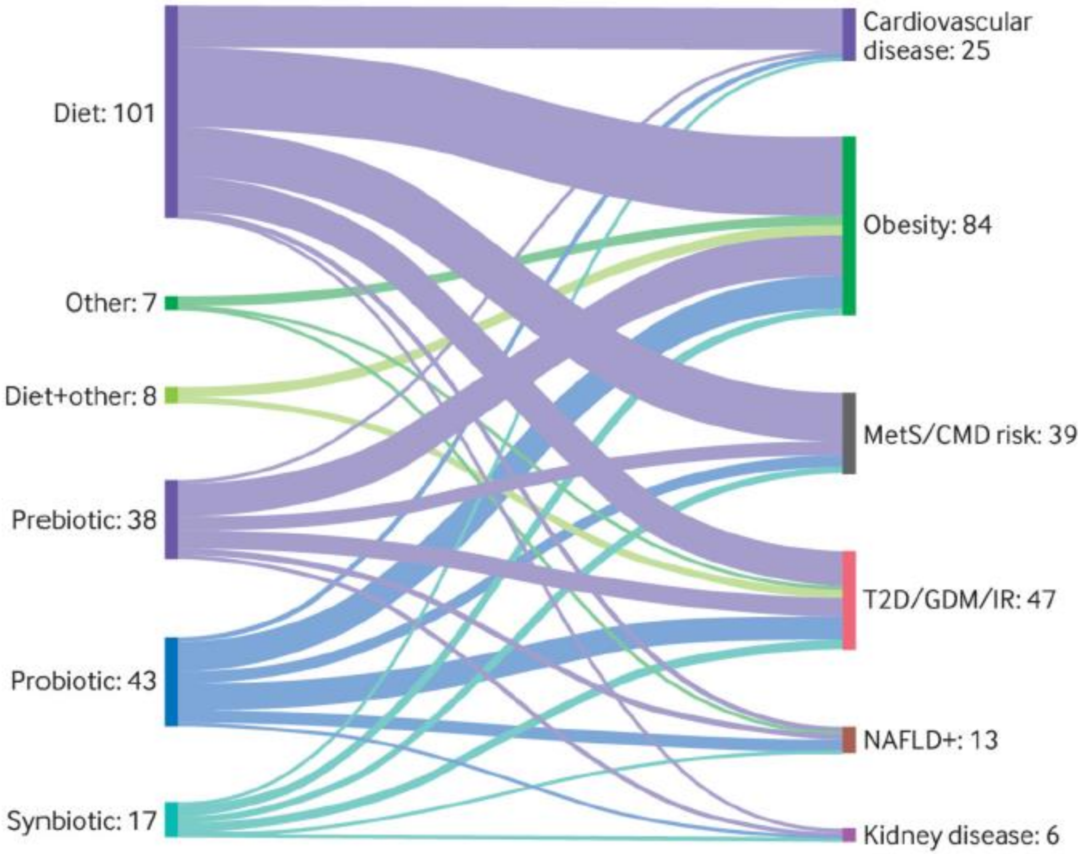


Region-specific distribution of trials



- Location of trials predominantly in EU > North America > China
- No representation from South Asia and Africa !!

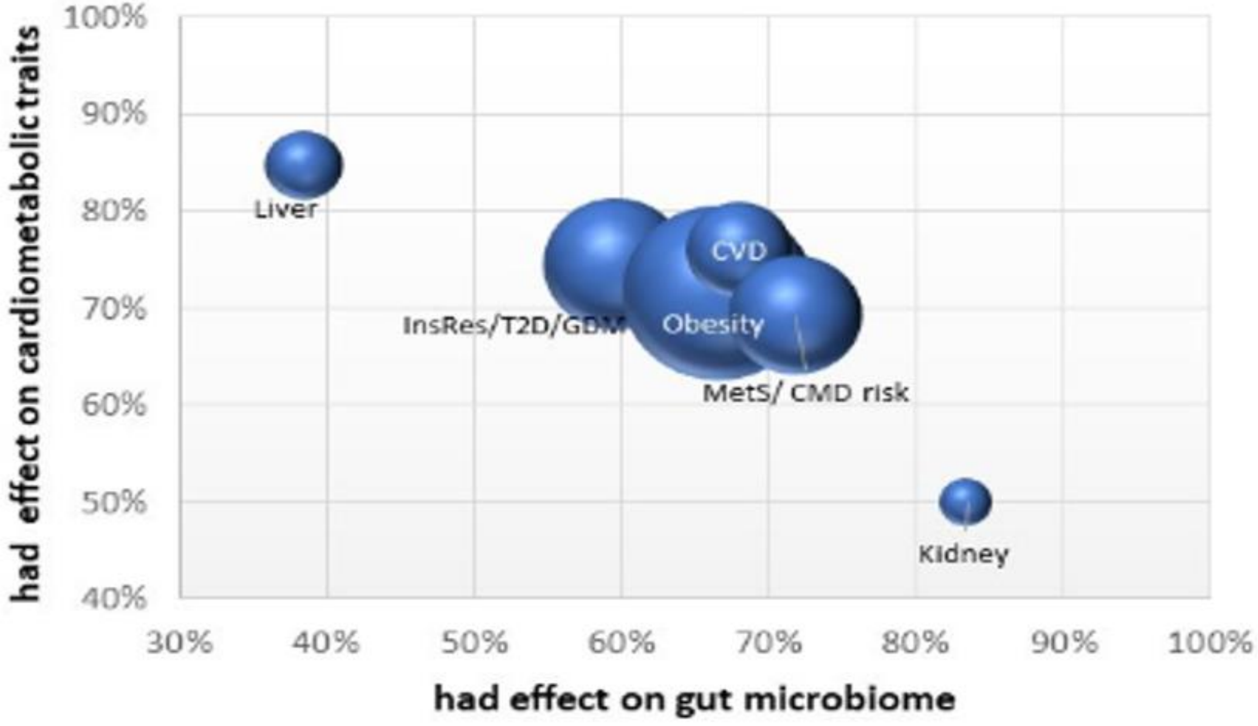
Majority (51%) involved dietary interventions and were focused on Obesity



Interventions are mostly still seen as extensions of nutrition and "healthy-eating" regimes, not as medical interventions for a given clinical condition

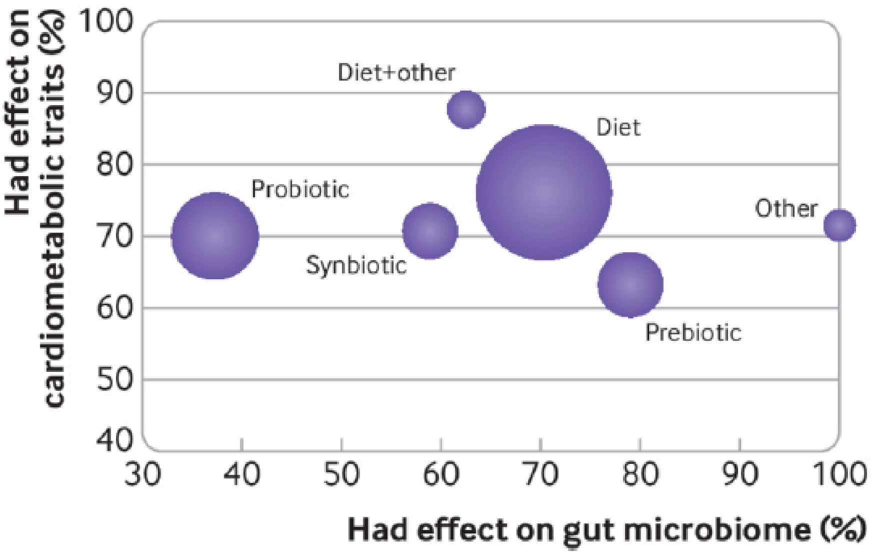
Gut microbiome is primarily a read-out in many interventions

72.5% had efficacy with respect to host clinical outcomes and 63.% had significant effects on the gut microbiome



The pattern was invariant across targeted conditions, with minor exceptions of Liver and Kidney Diseases

There were variations in effect depending on the intervention type



Host-specific Effect

Prebiotics < Probiotic/Synbiotic < Diet +

Difference of efficacy between interventions with highest (Diet +) and lowest efficacy (Prebiotics) was marginal ($P < 0.094$)

Gut Microbiome Effect

Probiotics < Diet / Diet + < Prebiotic

Probiotics had significantly lower effect on the microbiome when compared to Diet & Prebiotics ($P < 0.034$)

No significant difference between single and multi-strain probiotic interventions

Probiotic colonization and action have been previously reported to be driven by baseline gut microbiome composition

Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features

Cell

Niv Zmora,[1,2,11] Gili Zilberman-Schapira,[1,11] Jotham Suez,[1,11] Uria Mor,[1,11] Mally Dori-Bachash,[1] Stavros Bashiardes,[1] Eran Kotler,[3,4] Maya Zur,[1] Dana Regev-Lehavi,[1] Rotem Ben-Zeev Brik,[1] Sara Federici,[1] Yotam Cohen,[1] Raquel Linevsky,[1] Daphna Rothschild,[3,4] Andreas E. Moor,[3] Shani Ben-Moshe,[3] Alon Harmelin,[5] Shalev Itzkovitz,[3] Nitsan Maharshak,[6,7,8] Oren Shibolet,[6,7,8] Hagit Shapiro,[1] Meirav Pevsner-Fischer,[1] Itai Sharon,[9,10] Zamir Halpern,[6,7,8,12,*] Eran Segal,[3,4,12,*] and Eran Elinav[1,12,13,*]

Metagenomic analysis reveals distinct patterns of gut lactobacillus prevalence, abundance, and geographical variation in health and disease

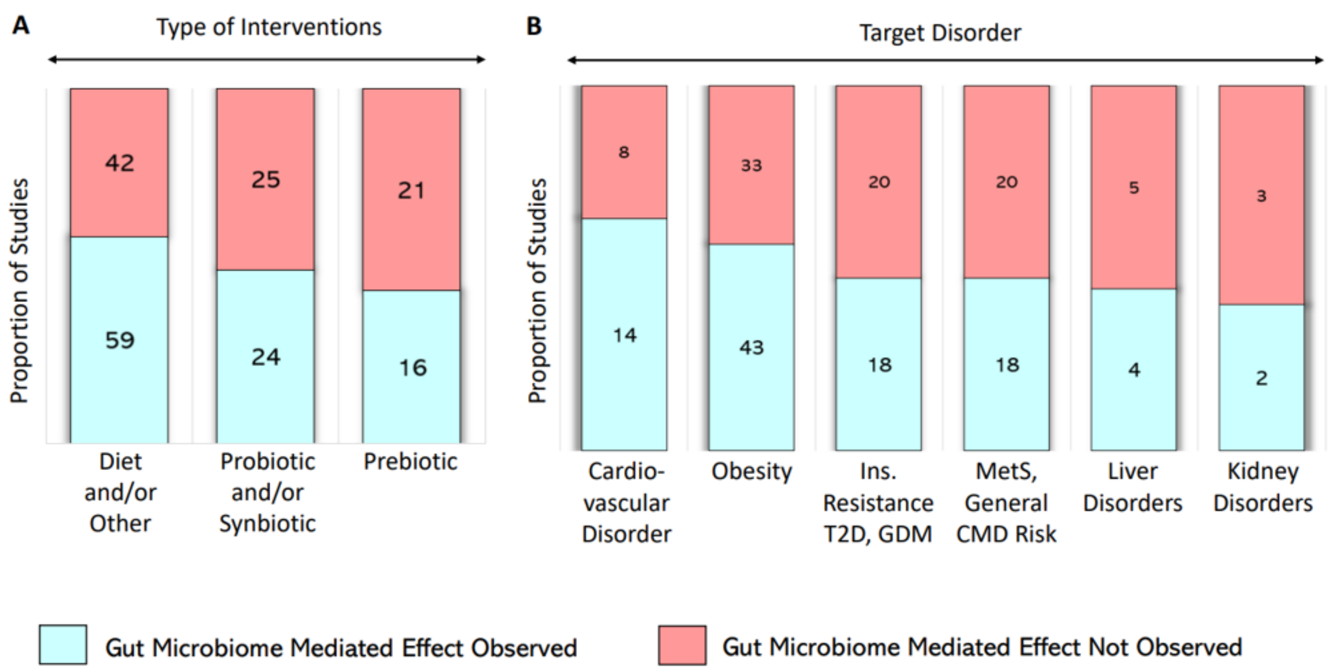
gut microbes

Taylor & Francis
Taylor & Francis

Tarini Shankar Ghosh, Jerome Arnoux & Paul W. O'Toole

Gut microbial changes mediating effects of cardiometabolic health

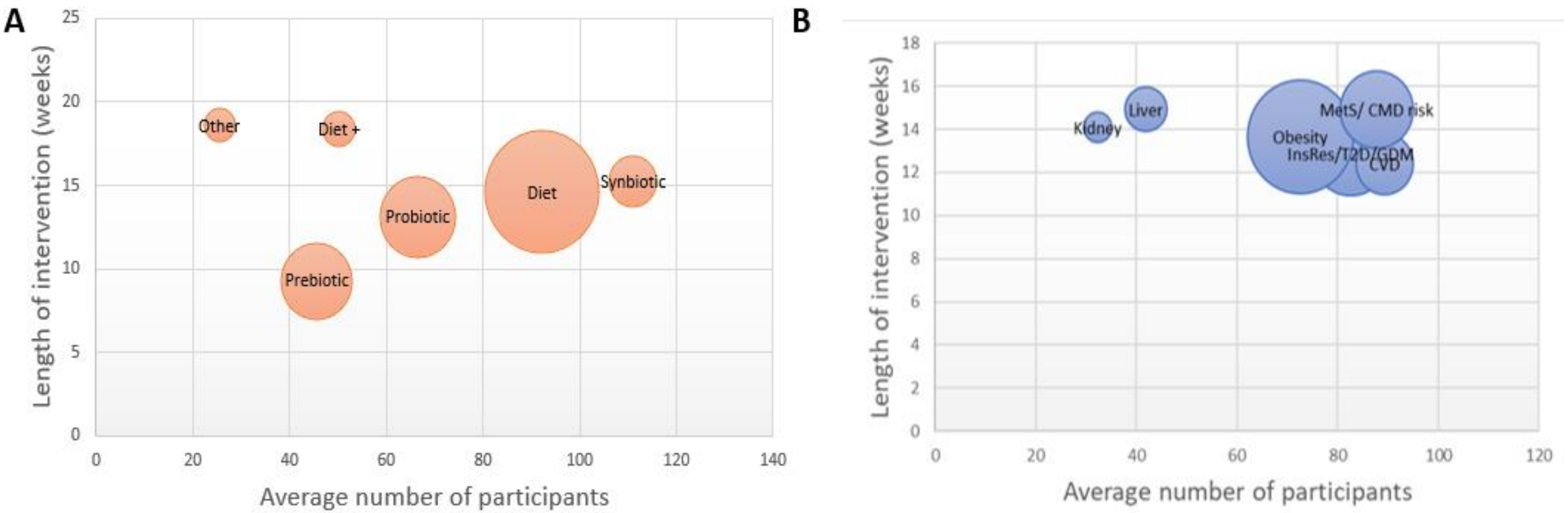
- In studies reporting significant changes in host phenotype, 63% reported these (or additional) effects to be mediated by gut microbiome changes



- Minor variations across intervention types and clinical conditions

- No uniform strategy to measure these effects, ranging from associations to mediation models to Machine learning models

There were also variations in the cohort size and duration of the interventions



Prebiotic interventions had noticeably lower mean length of interventions and smaller cohort size

May result in lesser power and effect of intervention trials

Summary of findings

- 72.4% of studies reporting significant improvements in one or more cardiometabolic traits
- Interventions tackling cardiovascular or organ specific diseases (such as atherosclerosis, hypertension, and non-alcoholic fatty liver disease), not just obesity, is fairly modest in proportion.
- Large geographic disparity exists in the location of these trials
- Probiotic interventions are less effective in improving the gut microbiome than broader interventions like diet and prebiotic that target multiple resident gut microbiome members simultaneously
- Lack of unified cohort, study design and effect measurement protocols

Future Directions

- Better candidate probiotics derived from resident gut microflora, e.g Akkermansia and Faecalibacterium

- Mechanistic Multi-OMIC level investigations to generate a robust microbial metabolite markers of cardiometabolic risk

- Well-designed large studies involving functional investigation and integration of multiple host phenotypic data

- Formulation of efficient integrative data-investigation strategies to probe host-diet-microbiota interactions

Acknowledgements

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Swiss Re

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