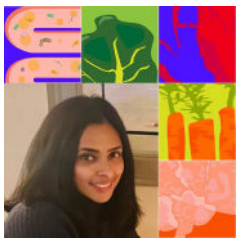
10/10/2023

Microbiome, Gut and Systemic Health: New Frontiers in Personalised Nutrition



Dr. Amrita Vijay

Practical Considerations when Designing and Interpreting Human Prebiotic and Probiotic Intervention Studies

12:00-12:45pm

An event by: Nutritional Medicine Institute

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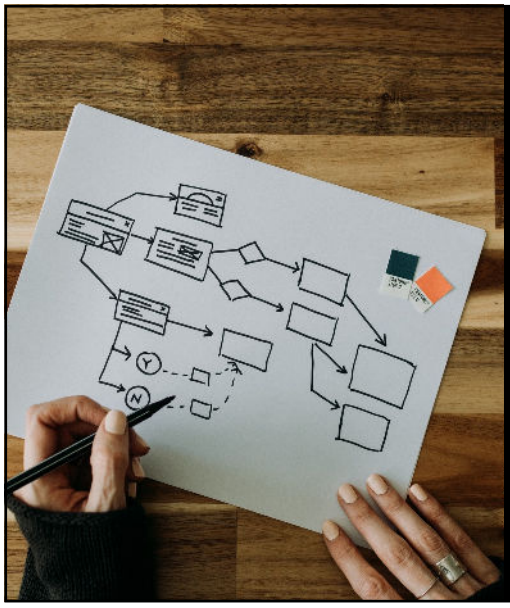
1



The design and interpretation of dietary intervention studies

Practical considerations when designing and interpreting pre and probiotic intervention studies in humans

Dr Amrita Vijay (PhD), Research Fellow
University of Nottingham

2

Conflict of interest

No conflict of interest to disclose as part of this presentation

3

This presentation will provide a practical overview for designing and interpreting human intervention studies targetting the gut microbiome

Key considerations include

- Diet-microbiome interactions
- Study design of diet intervention studies
- Interpretation of end points
- Current limitations and new insights

4

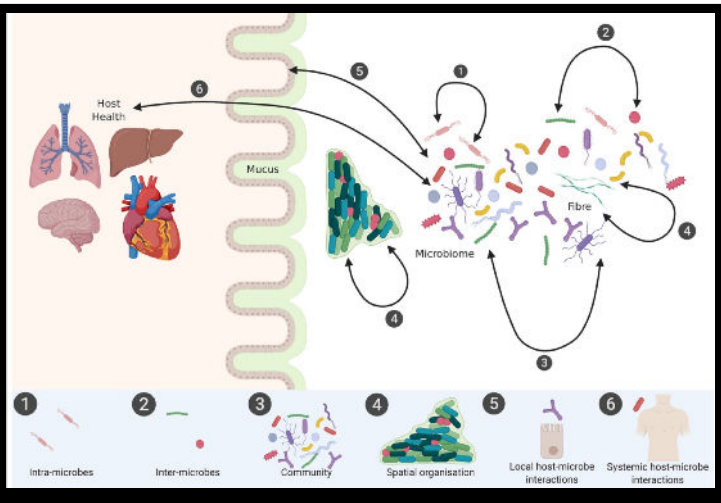
Dietary intervention studies can help generate important information

1 The effect of diet on the gut microbiome

2 The modifying effect the of gut microbiome on host health in response to diet

3 The level of variation in gut microbial metabolism of dietary constituents

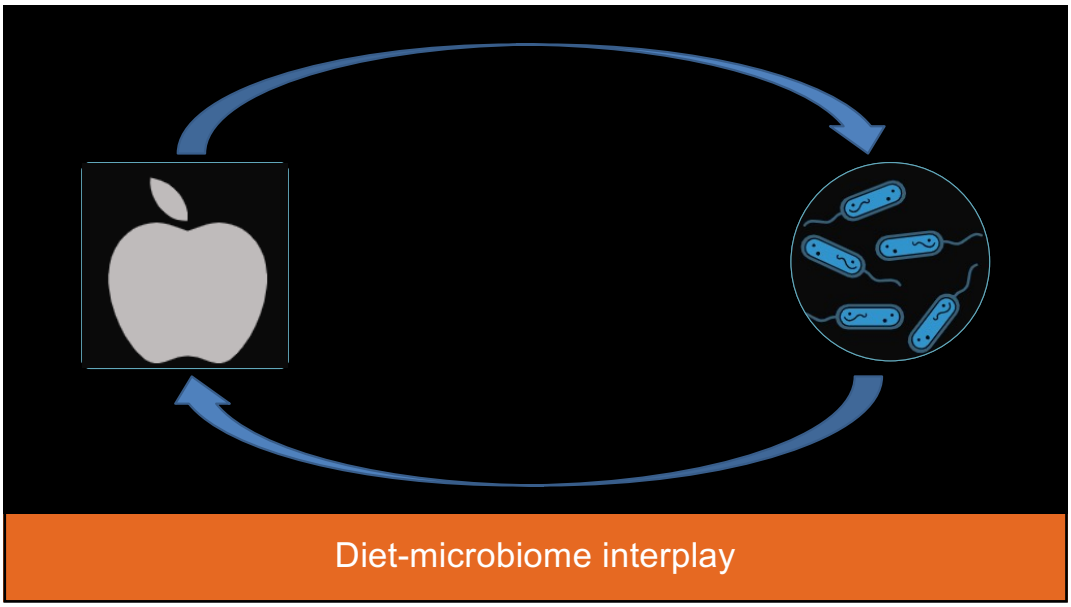
5



(Leeming et al., 2021)

The gut microbiome is a complex system with multiple interactions

6



7

Section 1

Design

8

Study Design

Single/double-blind, placebo-controlled trials

Parallel arm trials

Cross-over design trials

Careful study design considering blinding, duration, and confounds helps improve the quality of human intervention studies

9

Subject Selection

Inclusion & exclusion criteria

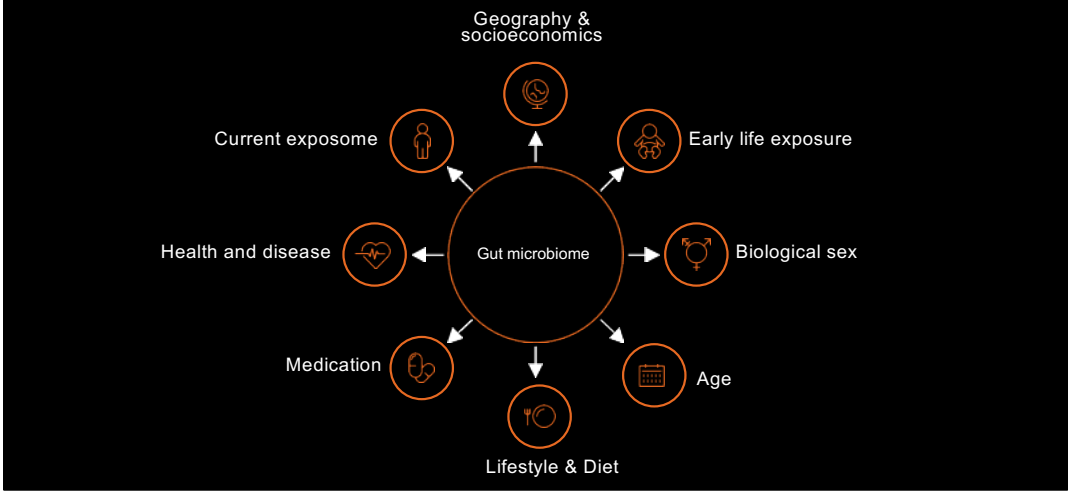
Screening

Baseline characteristics

Thorough screening and baseline data collection of study participants is crucial to ensure patient safety and enable morer accurate analysis of outcome measures

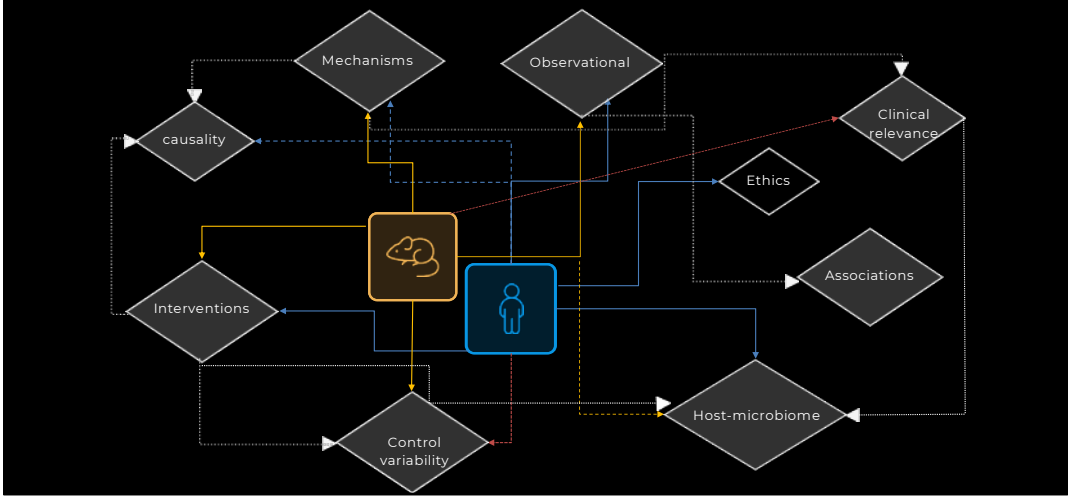
10

Confounding factors



11

Animal versus human model systems



12

Current approach

Randomised based on eligibility

Dietary intervention

Outcomes
(heterogenous)

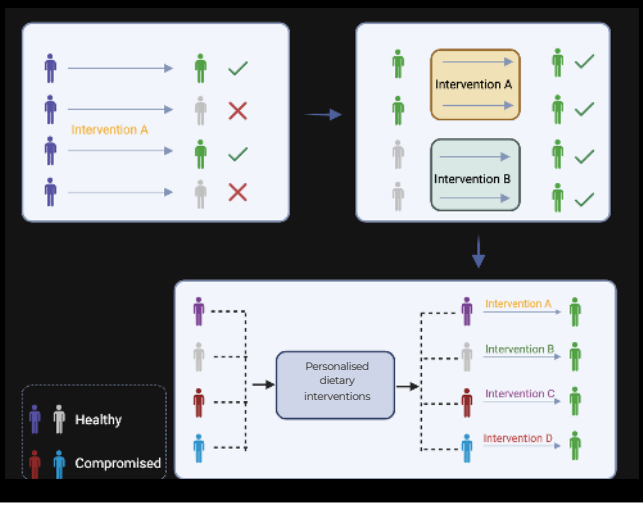
- Subjects are randomised into fibre intervention / placebo arm
- Collection of baseline data including habitual food intake
- Data/sample collected over limited number of time points during the course of the intervention
- Outcomes are heterogenous and in-consistent across similar studies
- Concept of 'permissive' and 'restrictive' microbiomes or 'responders' and 'non-responders' as a possible explanation for differences in receptiveness

(Leeming et al., 2021; Wu et al., 2011)

13

Ideal approach

Stratification based approach



(adapted-Liu et al., 2020)

14

Section 2

Interpretation

15

Common questions

1. What effects do diets, foods or food constituents have on gut microbial composition and/or activity
2. What effect does the gut microbiota have on the metabolism and bioavailability of nutrients present in foods
3. What effects do changes in the gut microbiota composition and/or activity following a dietary intervention have on functional metabolites

16

Data Analysis

Nature of datasets

Microbiome data are compositional in nature with specific features

Statistical tests

Use appropriate statistical tests informed by study design & outcome measures

Confounders

Account for confounding variables

Careful data analysis allows determining the true impact of an intervention

17

Endpoints measures

Microbiome composition

Assess changes in the types and abundances of gut microbes before and after intervention

Functional metabolites

Changes in gut derived (SCFAs) & host-derived- Metabolomics

Biomarkers

Changes in biomarkers of health & disease

Disease endpoints

Evaluate clinical measures of disease activity and severity, if studying a specific condition

Key endpoints provide insights into mechanistic changes in the gut microbiome, host physiology and potential clinical benefits on disease states

18

Factors that influence endpoints

Sample size
Informed by power calculations based on outcome of interest and existing data

Dosage & duration
The duration of the prebiotic/probiotic intervention should be long enough to observe potential effects

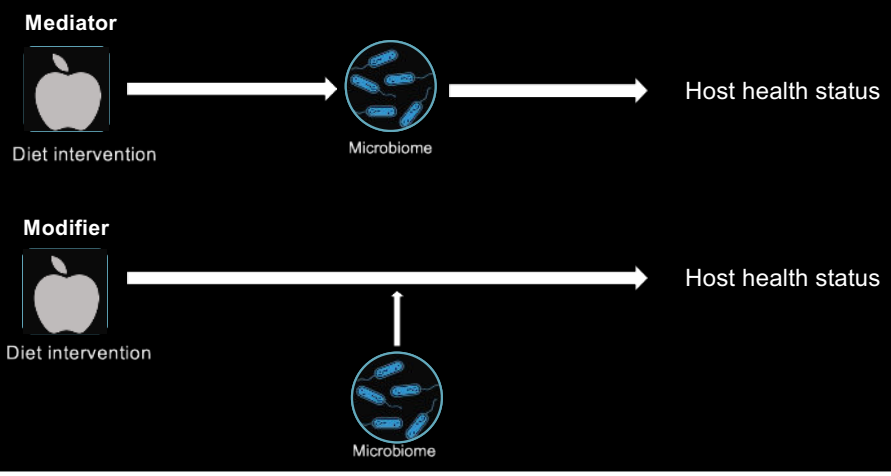
Compliance
Participant compliance can vary based on dosage, duration, study population

Cohort heterogeneity
Genetic and lifestyle differences among populations and individuals

Considering sample size, optimal dose/duration of the intervention may help improve the robustness of intervention

19

Microbiome mediated outcomes



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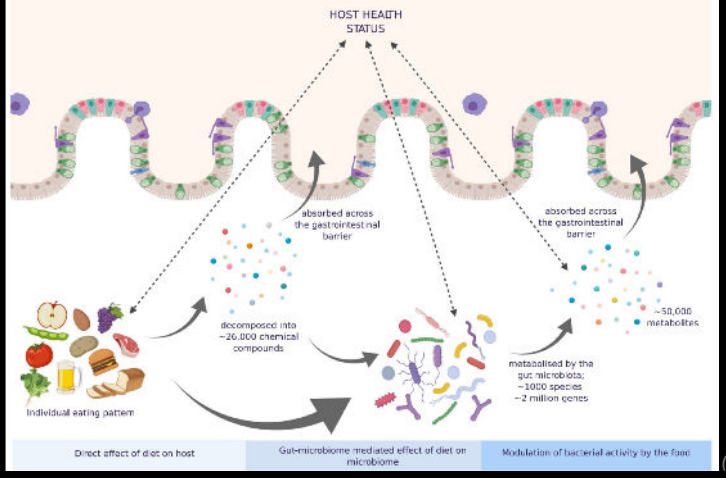


(Leeming et al., 2021)

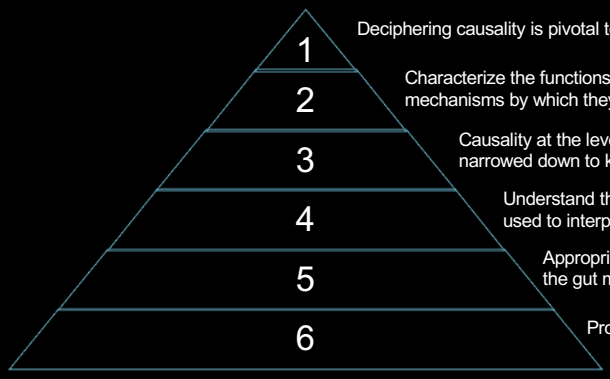
Diet- microbiome interactions mediating host health

21

22

Conceptual framework

To establish a causal link between diet, gut microbiota and health



Deciphering causality is pivotal to putting gut microbiota into the clinical setting

Characterize the functions of the strains of interest and to elucidate the mechanisms by which they interact with host tissues

Causality at the level of the whole-gut microbiota will need to be narrowed down to key players at the strain level

Understand the gut microbiota as an ecosystem which can be used to interpret dietary effects

Appropriate experimental design that explicitly implicates the gut microbiome as a causative agent of dietary effects

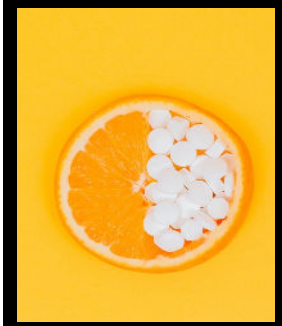
Proof of causality starts with correlative evidence

(Lam et al., 2018;Hughes et al.,2019;Wu et al.,2021)

23

Targetted interventions

Experimental design that explicitly implicates the gut microbiome as a causative agent of dietary effects



- Prebiotics/ dietary fibers as the sole contributor to any observed effects
- RCTs in which added fermentable carbohydrates are the only dependent variable could imply a causative role for the gut microbiome in any measured clinical benefits
- Combination of compositional and functional changes (metabolomics) could provide mechanistic insights
- Inferring causality may not, however, be that obvious for most dietary interventions that modulate both the gut microbiota and other host pathways

Transplantation of gut microbiota into germ-free mice, for example, is one of the best existing models with which to demonstrate causality in such cases

24

Gut microbiota as an ecosystem

Understand the gut microbiota as an ecosystem which can be used to interpret dietary effects

- The interactions in a microbial community can be on very different spatial and temporal scales that define the structure and function of a microbial network
- Some members rerferred to as "foundation species" are far more resilient to change than others
- Significant microbiome shifts can take a matter of weeks and months, rather than days in response to dietary interventions
- Identifying the presence and absence of strongly interacting species that could be integral to driving molecular changes.

The microbiota that make up the gut ecosystem do not exist in isolation but they interact and work with each other

25

Identification of key players

Causality at the level of the whole-gut microbiota will need to be narrowed down to key players at the strain level

- Moving away from diversity index and taxon-based associations into identifying specific strains having distinct functionalities and mechanisms of action
- Bacterial strains in the same taxonomic group have been found to vary in their relationships with the host bio-clinical parameters
- Among individuals whose guts were colonized by the same species, only 3.67% of the strains were common
- Importance of the interrelationships between predominant bacterial strains and observed distinct patterns of co-abundant changes in response to dietary interventions

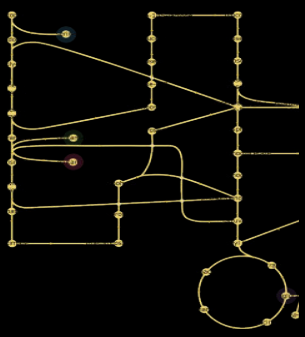
Identifying bacterial candidates associated with specific health outcomes and disease phenotypes

(Wu et al., 2021)

26

Functionality of the strains of interest

Identify functions of the strains of interest to elucidate the mechanisms by which they interact with host tissues



- In sickness and health: the ups and downs of *P. copri* in the human host
- Some strains of *P.copri* can degrade carbohydrates and fibers, others can biosynthesize branched-chain amino acids (BCAAs) from meat-based diets highlighting its functional diversity
- The diversity within the *P. copri* complex could be a clue to the *P. copri* paradox in health and disease states
- Reference to just one reference strain of *P.copri* limits the exploration of the genomic and functional diversity of other *P. copri* strains

Important to characterize the functions of the strains of interest and to elucidate the mechanisms by which they interact with host tissues

(Abdelsalam et al., 2023)

27

Translating gut microbiome research into clinical applications

Deciphering causality is pivotal to putting gut microbiota into the clinical setting

- Demonstrating the causative role of the gut microbiome in human health and diseases
- Diet is very powerful in changing the gut microbiota (for better or worse) and studies of dietary effects may be an important approach for understanding causality in regard to the gut microbiome
- Identifying the key strains that mediate microbe–host interactions and understanding their functionality
- Understanding the full influence of metabolites on host health

28

Key Takeaways

Study design is critical

Make sure to have adequate sample size, appropriate controls, randomization, blinding, etc.

Factoring confounding factors

Control for variables like age, gender, diet, etc. that could impact results.

Differentiating causality & association

Interpretation should be based on study design, analysis type and endpoint measures

Acknowledge limitations

Gaps in the field of microbiome research should be considered during design and interpretations

Following best practices in study design, interpretation of end points and acknowledging currrent limitations is key to high-quality human intervention studies

29

Thank you!

Nutritional Medicine Institute

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UKRI Medical Research Council

NIHR | Nottingham Biomedical Research Centre

30

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31

10/10/2023

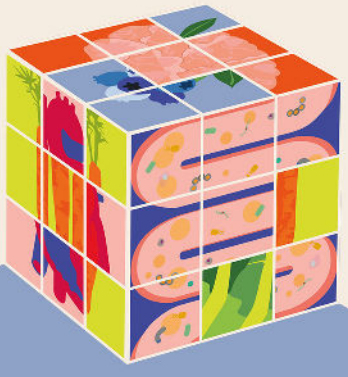
Microbiome, Gut & Systemic Health:

New Frontiers in Personalised Nutrition

NMI SUMMIT 2023

Saturday 14th October

Featuring Dr. Gerard Mullin, Professor Glenn Gibson, Dr. Amrita Vijay, Justine Bold, Dr. Jonathan Sutton and Benjamin Brown



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32