metagenopolis
mgps.eu

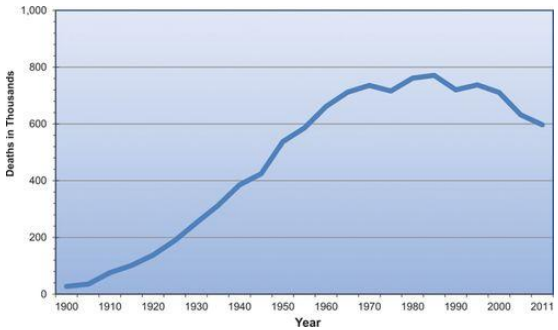
Microbiome and metabolome features of the cardiometabolic disease spectrum

MetaCardis

by INRAE

Scientific context

- Most common chronic non-communicable diseases involve a complex interplay between polygenic susceptibility, aging, sex and a multitude of environmental exposures.
- Environmental components (diet, …) exert some of their pathogenic impact via modification of the intestinal microbiome.
- Present study is focused on ischaemic heart disease (IHD), a leading cause of mortality worldwide.
- Disease-specific microbiome and linked metabolome features need to be separated from confounders introduced by pre- and co-morbidities and by multifactorial treatment.



Mozaffarian, D. *et al. Circulation* 2015

Metacardis consortium

14 Partners all around Europe

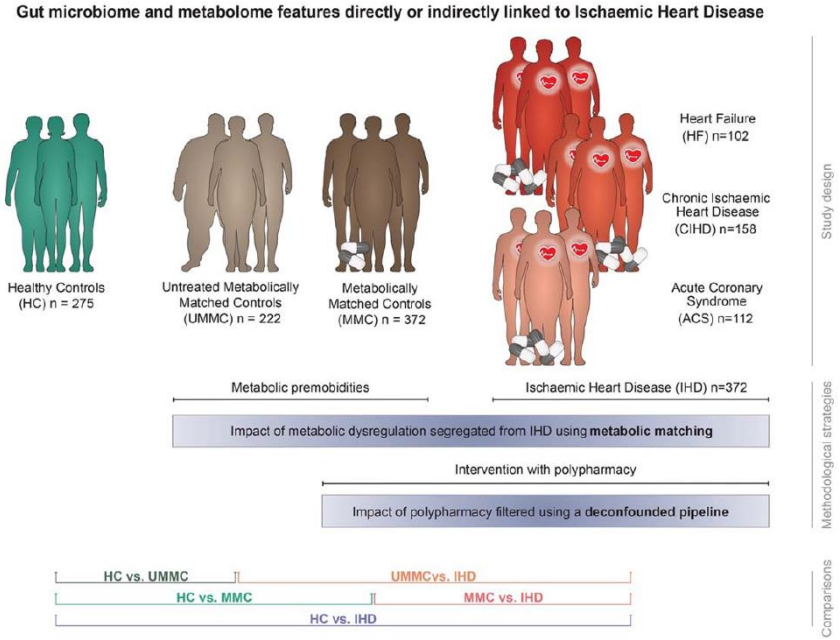
Scientificaly recognized PIs

- Dusko Ehrlich
- Karine Clement
- Oluf Perderson
- Peer Bork
- Marc-Emmanuel Dumas

Metacardis cohorts

Group 8 (n= 277)	Group 1 RH (n=43)	Group 1 (n= 252)	Group 2A (n= 248)	Group 2B (n= 139)	Group 3 (n= 552)	Group 4 (n= 111)	Group 5 (n= 159)	Group 6 (n= 98)	Group 7 (n= 21)
The **control group**, including participants with a BMI <25 that did not present the metabolic syndrome, were not diabetic, and did not have coronary heart disease.	The **rather healthy group**, including participants with a BMI ≥ 25 and < 35 but without any cardiometabolic condition	A group of participants without diabetes or coronary heart disease, but with the **metabolic syndrome**	Participants with **severe obesity** (BMI ≥35) that were neither diabetic nor suffering from coronary artery disease	Participants that were **candidates for bariatric surgery**, i.e. with a BMI ≥35 and comorbidities, or a BMI ≥40	Participants with **diabetes** but without coronary artery disease	Participants with a **first event of coronary artery disease**	Participants suffering from **chronic coronary artery disease without heart failure** (i.e. presenting a left-ventricular ejection fraction ≥45);	Participants suffering from **chronic coronary artery disease with heart failure** (i.e. presenting a left-ventricular ejection fraction <45);	Participants suffering from **heart failure related to origins other than coronary artery disease**

Study design



➢ 6 different study cohorts

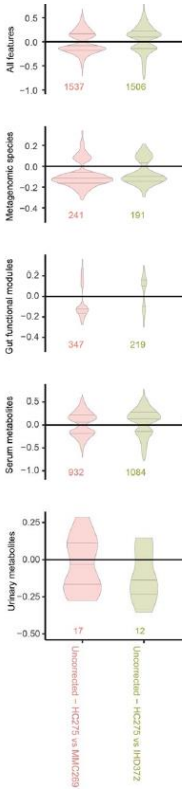
Multiple different omics:

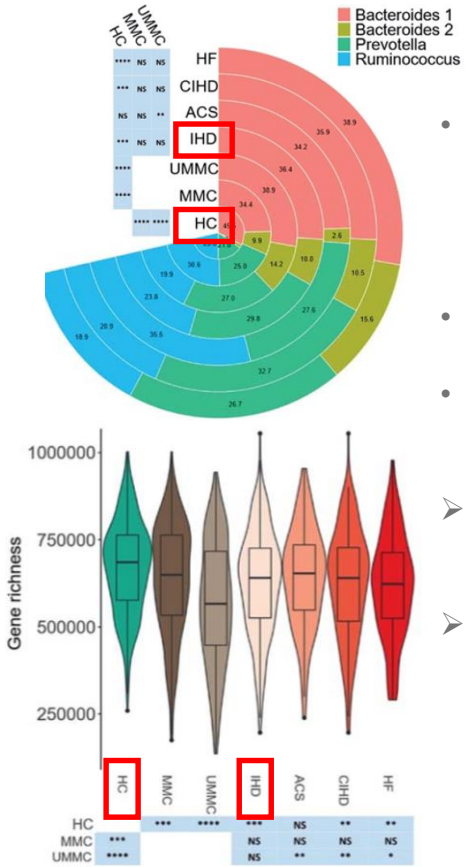
- Anthropometric measures
- Inflammatory parameters
- Drugs intakes
- Dietary measures
- Gut microbial diversity indexes, taxa and microbial functional modules
- Metabolites in fasting serum and urines

1 external validation cohort composed of acute coronary israeli patients (Talmer-Barkan *et al* , Nature medecine 2022):

- 629 metabolomic profils
- 540 metagenomic profils

Majority of microbiome and metabolome alterations happen long before IHD event



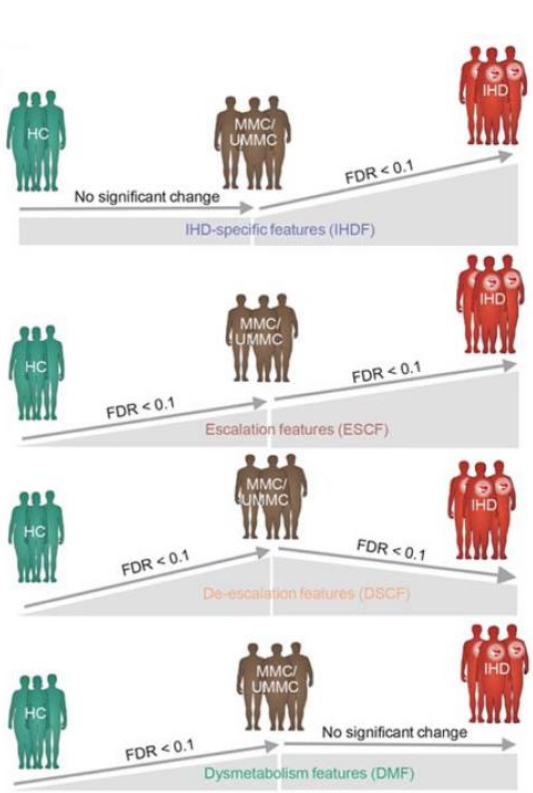


- Microbiome and metabolome differed between IHD and HC:
  - From *Bacteroides* 1 and *Ruminococcus* enterotypes towards the *Bacteroides* 2 as disease worsened.
  - Loss of microbial gene richness in MMC and IHD.
- ….BUT comparing HC to MMC revealed even more differential features….
- … AND higher discriminatory potential between IHD and HC than between IHD and MMC. Most of the features are already significant in MMC.

➢ Studies erroneously reported dysmetabolism features as IHD features. They may contribute to increased risk of IHD but are not specific for IHD.

➢ Major shift in gut microbiome and metabolome during the dysmetabolic stage prior to IHD diagnosis.

Yet some alterations are specific to IHD



IHD specific

- 33 species IHD specific markers, mostly depleted in patients (65%): Proteobacteria, Acinetobacter, Turcimonas and Acetobacter, previously reported depleted in IHD.
- Enrichment of a range of IHD-specific metabolites:
  - Choline and carnitine intermediaries pathways including precursors of TMAO known to modulate IHD risk.
  - Phenylacetate derived metabolites.
  - Proinflammatory lipids derived from arachidonic acid (C20:4)
- Some fatty acid methyl esters depleted in IHD (ex: alpha tocopherol).

escalation

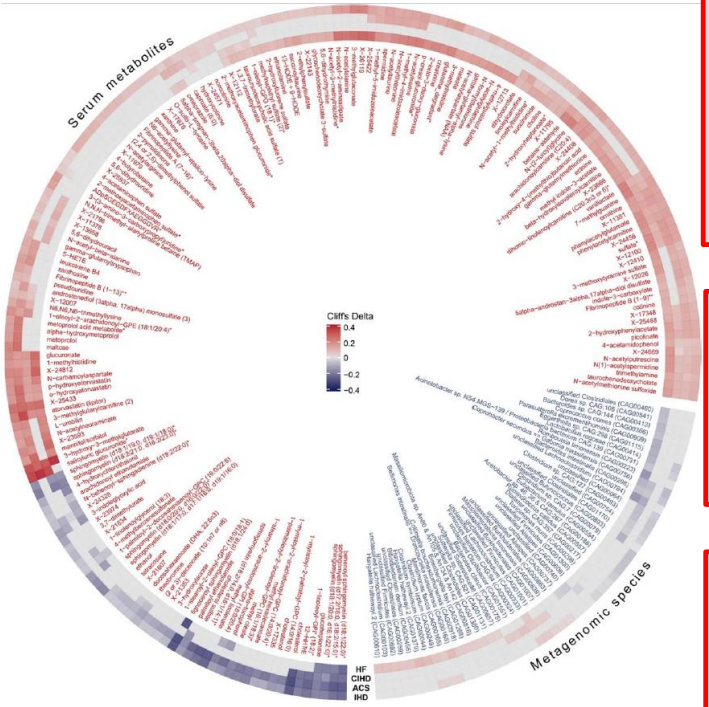
- Sphingomyelins, glycerophospholipis, some carotenoids and ergothioneine, known to improve cardiovascular health, following a depletion pattern.
- Glutathione metabolism, markers of oxidative stress, 4-cresol, and phenylacetylglutamine exhibited an enrichment pattern.

De-escalation

- Mostly initial depletion at the stage of dysmetabolism with reversal at the stage of treated IHD
- Catecholamine intermediates, bilirubin products, bile acids and odd-chain lipids with bacterial origin
- TMA production and butyrate production II.
- Responsiveness of both microbiome and metabolome features to long-term treatment plausibly contributing to stabilization of IHD.

Detailed analysis of IHD subgroups (ACS, CIHD and HF) groups provided more granularity

- Dysmetabolism diruptions persist throughout the various stages of IHD.



ACS

- Microbiome alterations related to dysmetabolism
- Metabolome perturbations beginning shortly before the ACS event:
  - increase of pro-inflammatory metabolites, products of phenylalanine metabolism (phenylacetylcarnitine, …) and TMA.
  - decrease of health beneficial metabolites alpha-tocopherol, ergothioneine, methyl oleate and methyl hexadecanoate.

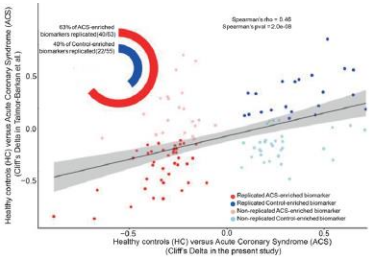
CIHD

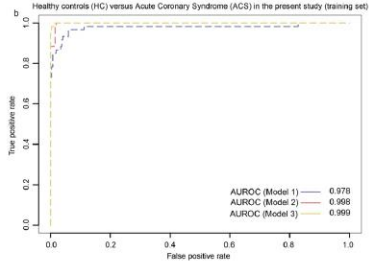
- Additional microbiome changes:
  - enriched potentials for BCAA and methionine biosynthesis
  - enhanced degradation of phenylalanine and tyrosine
- Increased abundance of methionine and related metabolites, associated with cardiovascular phenotypes.

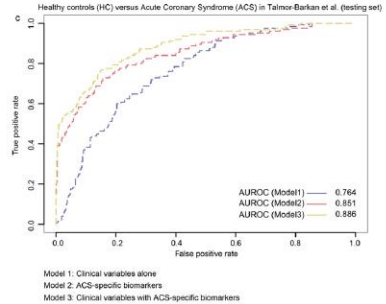
HF

- Additional microbiome changes
- Enrichment of 4-cresol and derived metabolites, choline and TMA
- Altered fatty acid metabolism (alpha-tocopherol, ergothioneine and 3-indoleglyoxylic acid depletion), known to play a crucial role in HF pathogenesis.

Major part of our observed IHD alterations validated in a external cohort







Model 1: Clinical variables alone
Model 2: ACS-specific biomarkers
Model 3: Clinical variables with ACS-specific biomarkers

- Models built with specific –omics markers yielded AUC systematically higher than models with clinical markers only.
- Combination of the two marker types did not improve classification relative to MMC

Talmor-Barkan dataset:

- Similar changes observed in the two studies
- Models based on our ACS-specific metabolome markers performed substantially better than models based on clinical variables alone.

Take home messages

- Major shift in gut microbiome and metabolome during the dysmetabolic stage prior to IHD diagnosis :
  - multiple species and microbial functional potentials like reduced SCFAs biosynthesis and increased BCAAs production.
  - low cell count *Bacteroides 2* enterotype in both MMC and IHD.

- IHD cases display:
  - depletion of fatty acid esters ergothioneine and alpha-tocopherol, known for vasoprotective and antioxidant properties
  - enrichment in TMA intermediates and tryptophan and phenylalanine derived metabolism.
  - 4-cresol and phenylacetylglutamine representatives of ESCF potentially mirroring disease severity.

- In the IHD subtype analyses:
  - dysmetabolism-related gut microbiome changes in ACS cases.
  - 45% of altered host metabolites in ACS cases unrelated to dysmetabolism.
  - alterations of the microbiome and metabolome specific for CIHD and HF
  - overwhelming role for microbial-host metabolism of aromatic amino acids derived from phenylalanine and tyrosine in the later stages of IHD pathogenesis.
- Better stratification IHD cases from HC and MMC with identified microbiome and metabolome features;

➢ considered modifiable targets in future preclinical and clinical IHD prevention trials.

Thank you for your attention