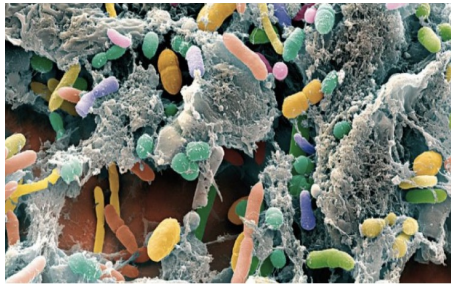
nutriomics

Nutrition & Obesities; Systemic approaches



Prof Karine Clément MD, PhD

NutriOmics Research Group (U1269)

INSERM, Sorbonne University

Pitié-Salpêtrière hospital, faculty of Medicine,

Karine.clement@inserm.fr

https://www.nutriomique.org

Microbiote and obesity : vitamins the neglected actors

ADeBIOTeCH
THINK TANK ONE HEALTH

Microbiote intestinal et prévention

Santé Humaine et Animale

Mardi 27 septembre 2022

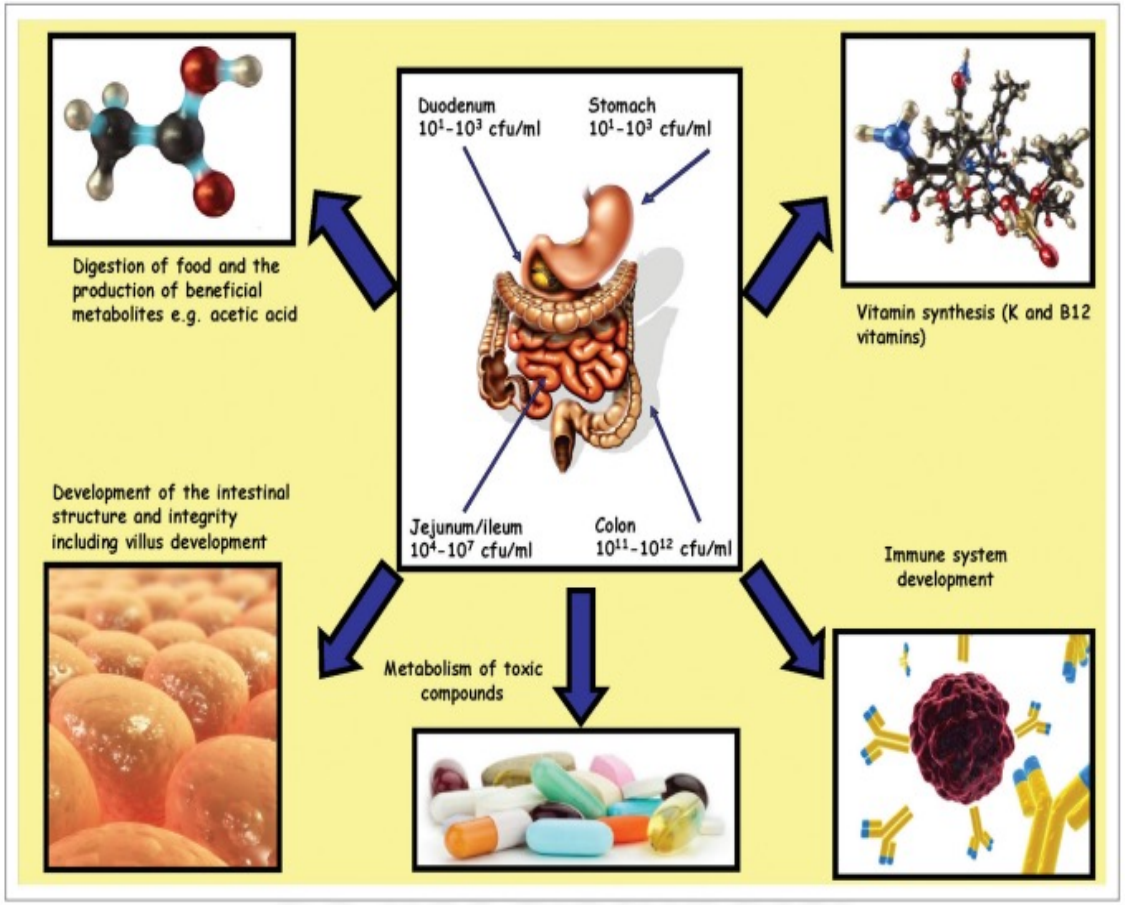
10h00 – 13h00

MÉDECINE SORBONNE UNIVERSITÉ

Inserm
La science pour la santé
From science to health

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

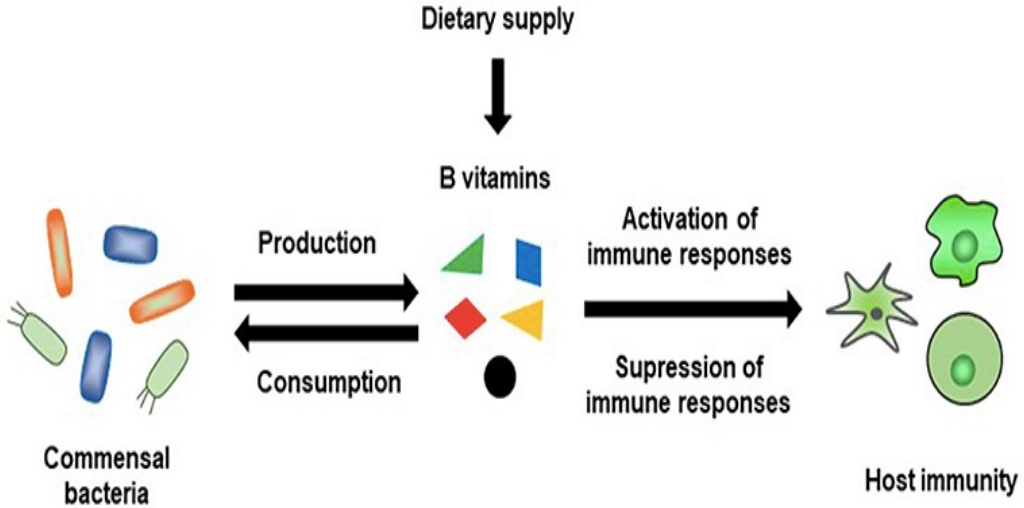
Vitamins B are key for metabolism and immunity



Importance of Gut Microbiota in Human Health

8 Known B vitamins

Vitamin B_1, thiamin.
Vitamin B_2, riboflavin (lactoflavin).
Vitamin B_3, vitamin PP (or niacin).
Vitamin B_5 , Pantothénique acid.
Vitamin B_6, pyridoxin.
Vitamin B_8, Biotine (Or B_7 in some countries).
Vitamin B_9, Folic acid
Vitamin B_{12}, Cobalamines.



Fouhy Gut microbes 2012;
Prakash et al; Journal of Biomedicine and BiotechnologyNature 2011

Yoshii, Frontiers in Nutrition, 2019

MetaCardis (**Meta**genomics in **Car**diometabolic **Dis**ease)

Study the impact of qualitative and quantitative changes in gut microbiota on the pathogenesis of cardiometabolic diseases and associated co-morbidities.

http://www.metacardis.eu

- Coordination INSERM: **Pr. K. Clément**
- 15 partners – 6 european countries – 3 companies
- Patient association (heart and obesity)
- 2012 -> 2018

- ✓ Transdisciplinary expertise
- ✓ Clinicians
- ✓ Microbiologists
- ✓ Immunologists
- ✓ Bioinformaticians - « omics » experts

Data source	Sample	#Patients
Clinical data		2100
Metagenomics		1973
Metabolomics		1955
Metabolomics		1900
Metabolomics		1844
Clinical follow-up		807

Touch, Faseb J, 2018
Viera-Silva et al, Nature 2020
Molinaro, Nature Comm, 2020
Bel Lassen, Nutrient, 2021
Forslund, nature 2021
Fromentin S, Nature Med, 2022
Belda, Voland et al, Gut, 2022

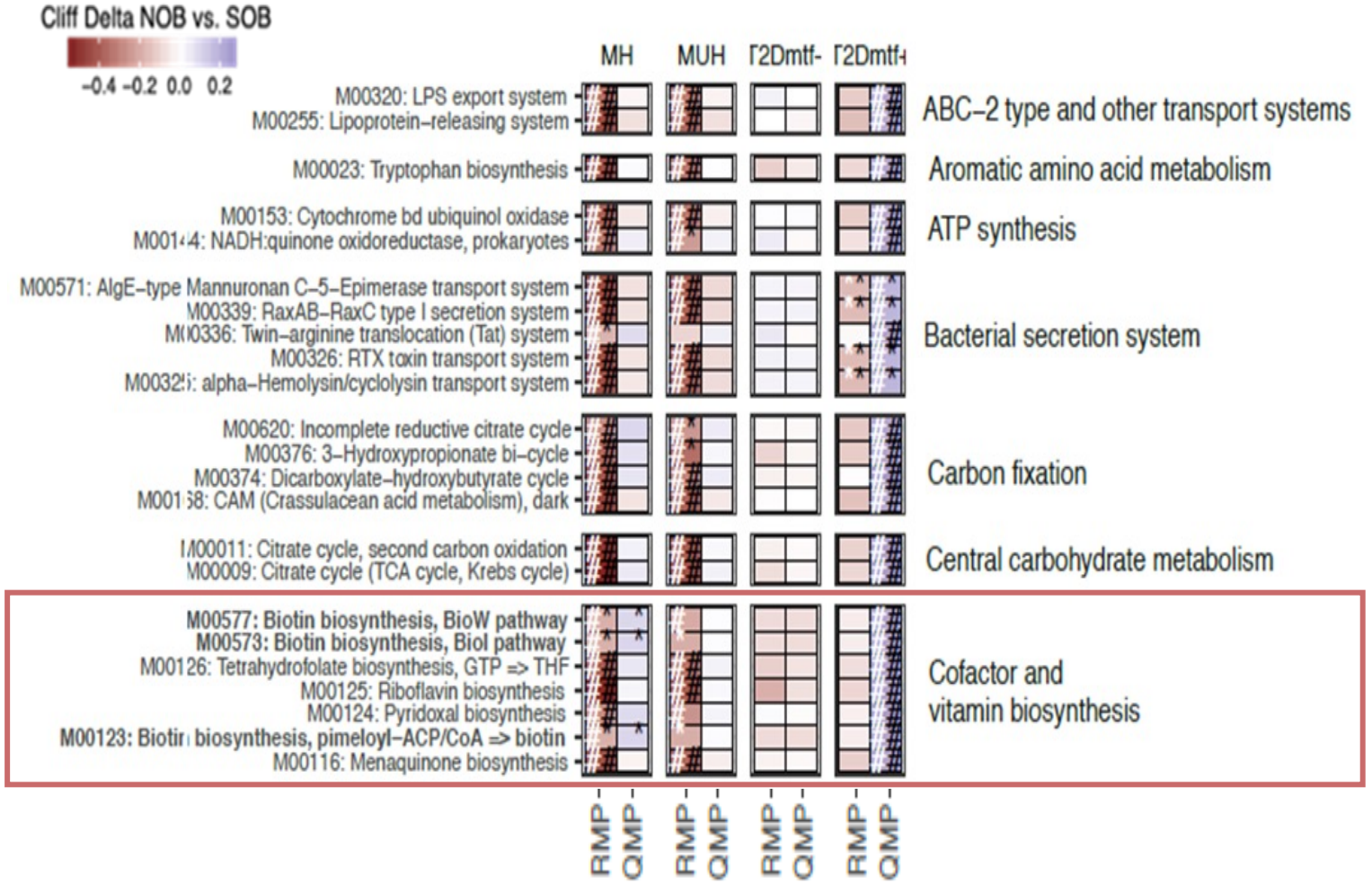
Establishment of a cohort of <u>2100 patients</u>
(healthy, obesity, type 2 diabetes, cardiovascular diseases)

Biotin alteration in severe obesity in humans

MH : Metabolically Healthy
MUH : Metabolically Unhealthy
T2D mf- : T2D without metformin
T2D mf+ : T2D with metformin

RMP: relative metagenomic profiles
*QMP: quantitative metagenomic profiles = RMP*cell density*

Gut microbiota profiling (n=1546)



- **Several microbial modules of B-vitamins biosynthesis including *biotin* are altered in severe obesity.**

MH: Metabolically healthy, MUH: Metabolically unhealthy, T2Dmtf: Type 2 Diabetes metformin – or +; NOB: non obese, SOB: severely obese

… Biotin metabolism in gut microbiota

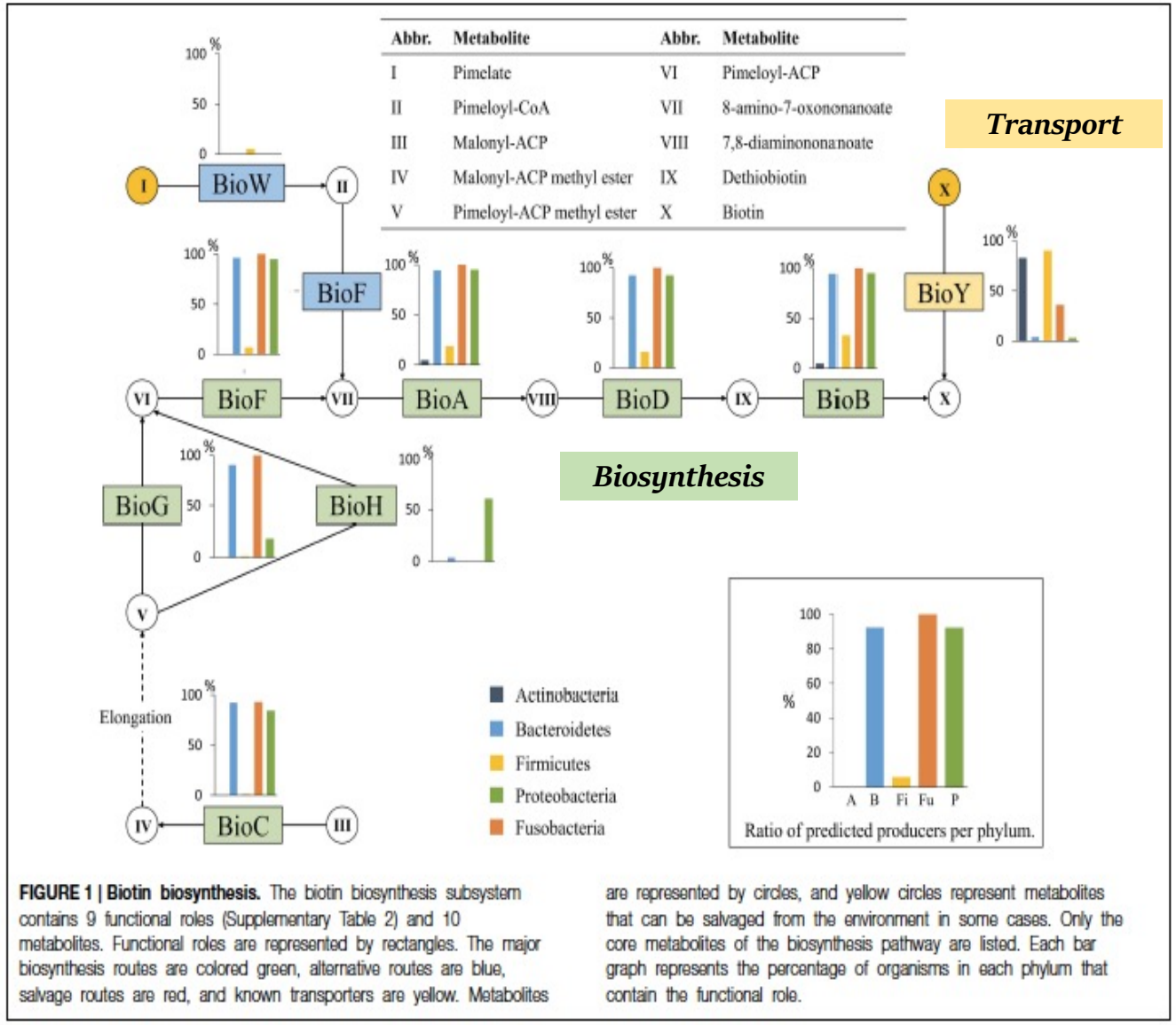


FIGURE 1 | Biotin biosynthesis. The biotin biosynthesis subsystem contains 9 functional roles (Supplementary Table 2) and 10 metabolites. Functional roles are represented by rectangles. The major biosynthesis routes are colored green, alternative routes are blue, salvage routes are red, and known transporters are yellow. Metabolites are represented by circles, and yellow circles represent metabolites that can be salvaged from the environment in some cases. Only the core metabolites of the biosynthesis pathway are listed. Each bar graph represents the percentage of organisms in each phylum that contain the functional role.

Magnùsdottir et al., 2015

- **B vitamins can be produced by the gut microbiota**

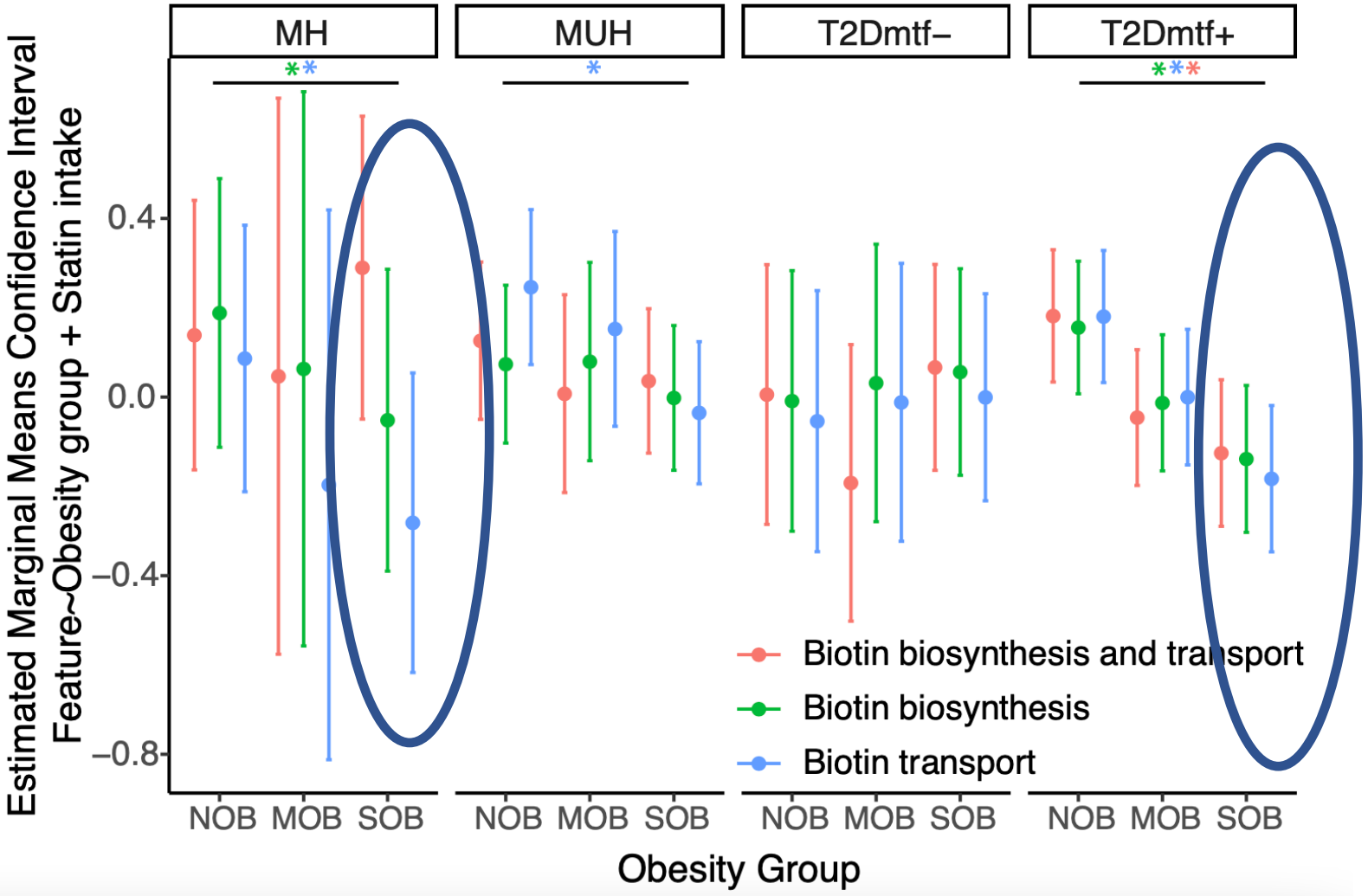
Biotin

Producers	Transporters (=Consumers)
Bacteroidetes Proteobacteria Fusobacteria	Firmicutes Actinobacteria

Eugeni Belda (IRD)

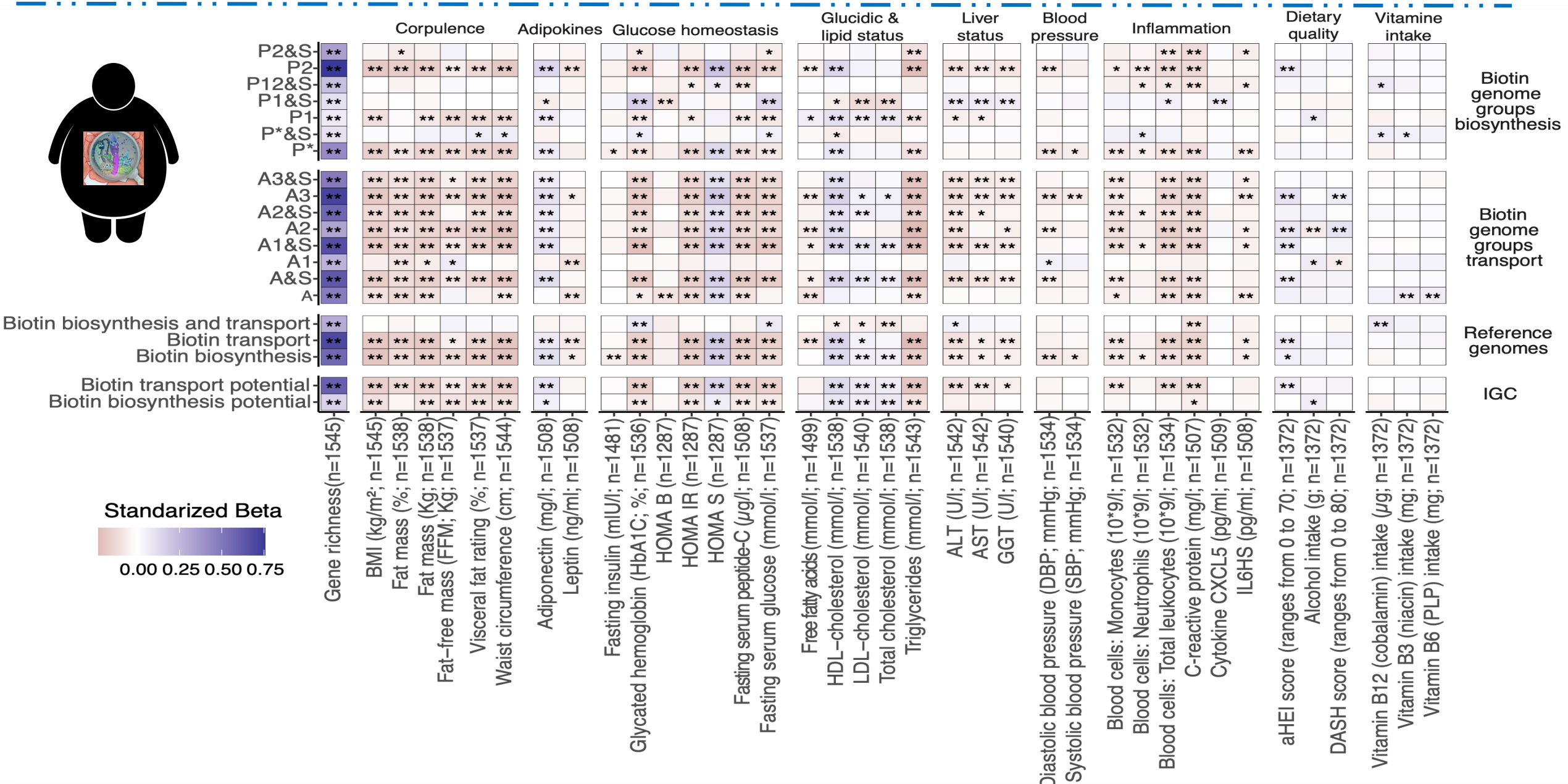
… Biotin transport and synthesis

MH : Metabolically Healthy
MUH : Metabolically Unhealthy
T2D mf- : T2D without metformin
T2D mf+ : T2D with metformin

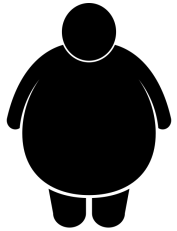


- **Bacterial Biotin metabolism is altered in severe obesity.**

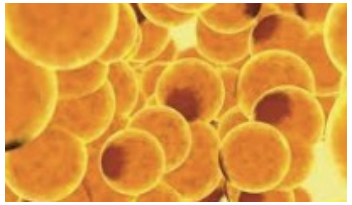
Association between bacterial biotin metabolism and host metabolism and inflammation



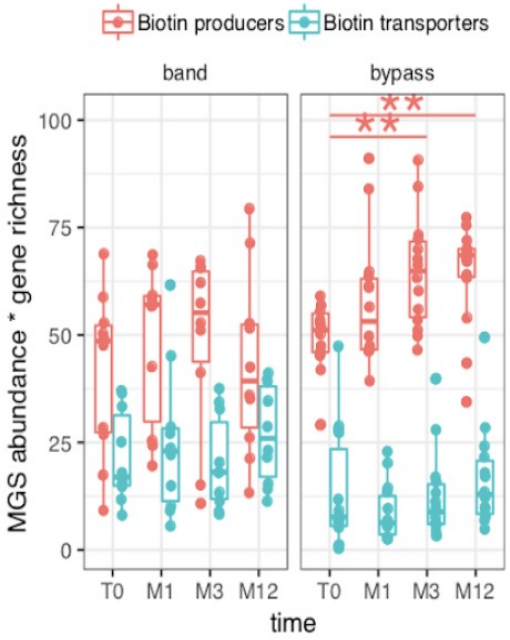
Biotin and-related carboxylases after gastric surgery

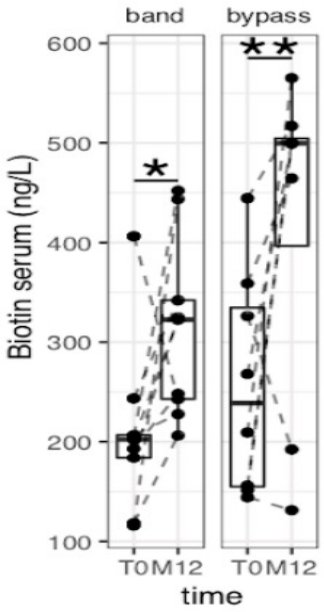


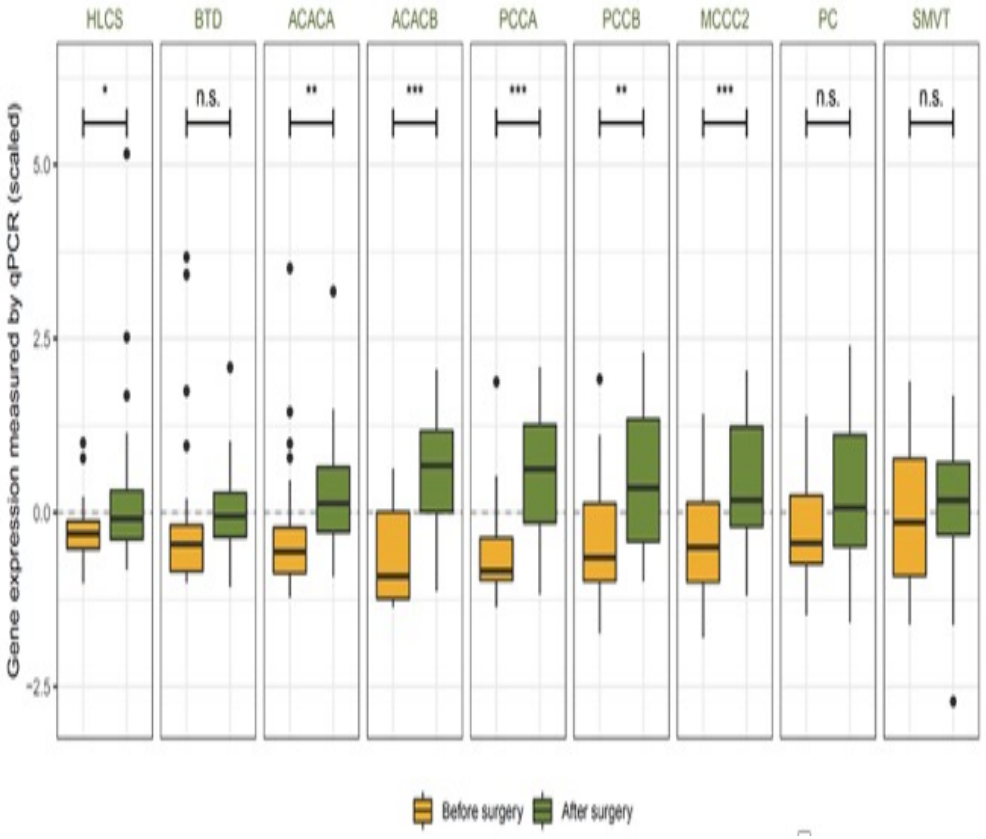
Gastric surgery



Gene expression (Adipose tissue)







- **Increase** of biotin-producing bacteria after the surgery.
- **Improvement** of proportion of patients with optimal biotin status one year after bariatric surgery

*Of note after bariatric surgery patients are **substituted by vitamins (including biotin)***

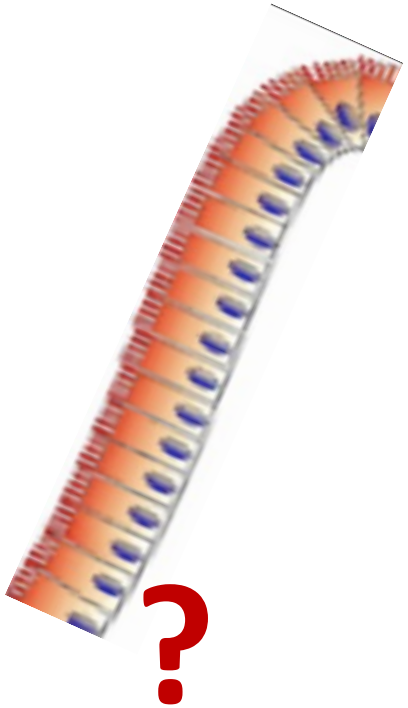
- Improvement of adipose tissue metabolism (reduced inflammation and increased carboxylase)

Biotin metabolism in Gut Microbiota & Severe Obesity ?

Gut Microbiota
(Severe Obesity & dysbiosis)

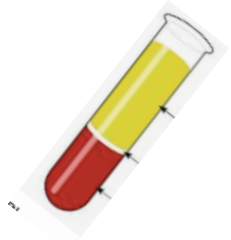
Default in Biotin synthesis &transport

Gut Barrier



Host

Severe obesity



Biotin

Biotin-dependant Carboxylase

Bypass

Origin of biotin deficiency in severe obesity ?

Can we modulate biotin metabolism in severe obesity ?

Eugeni Belda (IRD)

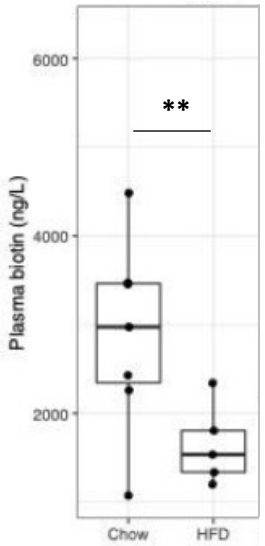
Lise Voland

Role of diet and weight modification (murine models)

Diet-induced Obesity

Chow

~0,3 µg biotin/mice/day

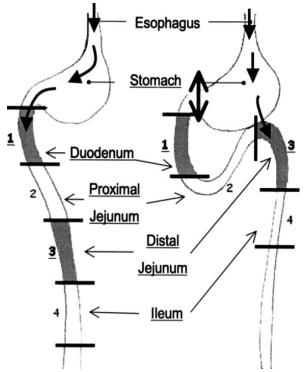


HFD

~0,65 µg biotin/mice/day

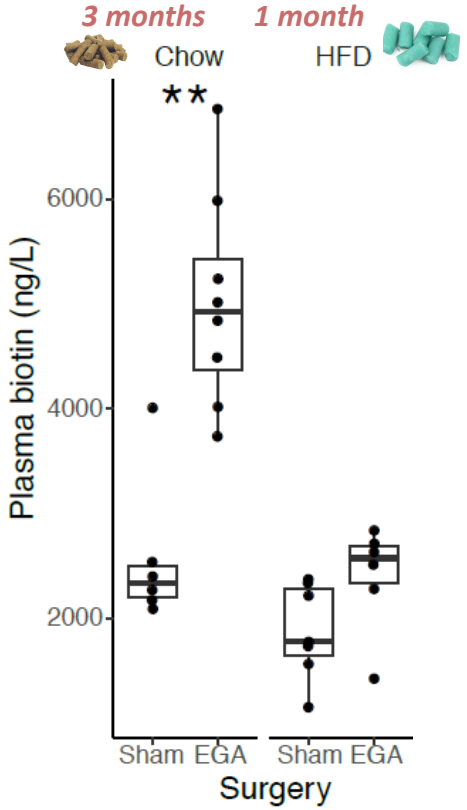
⇨**Biotin intake x2 in HFD**

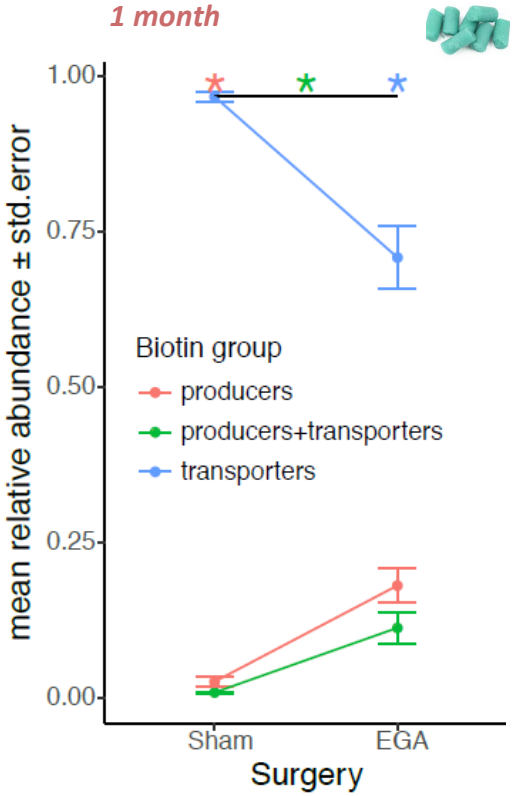
EGA



F. Andreelli
C. Amouyal

EGA: Entero-gastro-anastomosis





- **Decrease** of plasma biotin under HFD (despite higher intake)
- **Increase** of plasma biotin and bacterial biotin-producing potential after the surgery

** p<0,05, ** p<0,001, T-test*

Gut microbiota and circulating biotin levels

Chow

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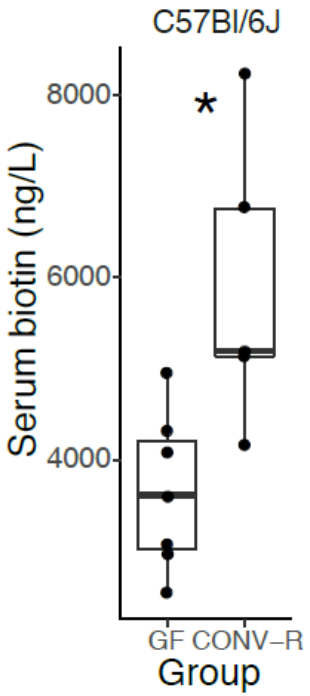
Germ-free (2 models)



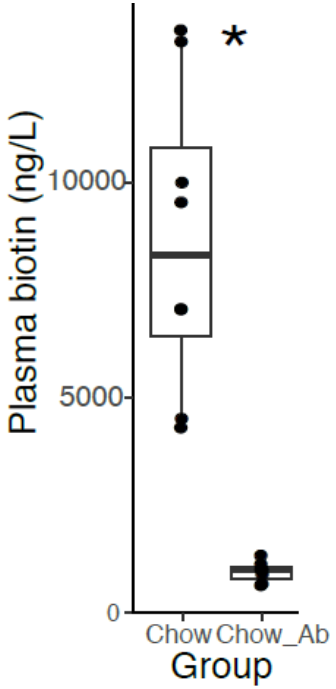
Chow

100 mg/kg

200 mg/kg

Vancomycin
Metronidazole
Neomycin
Ampicillin

Daily gavage for 14 days

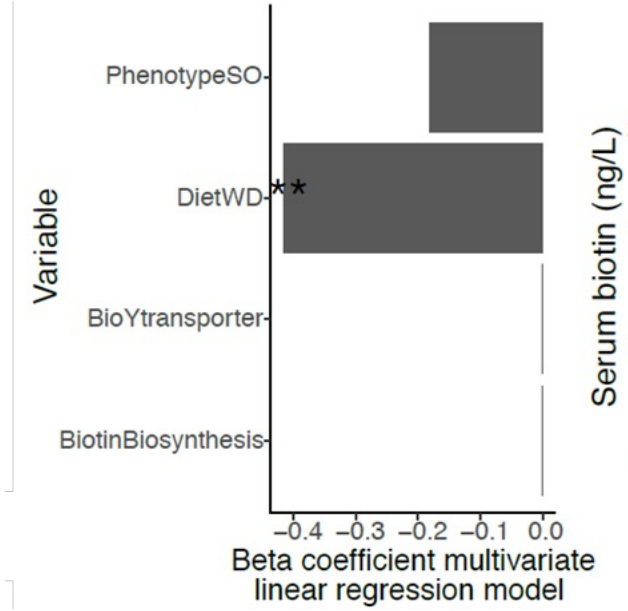


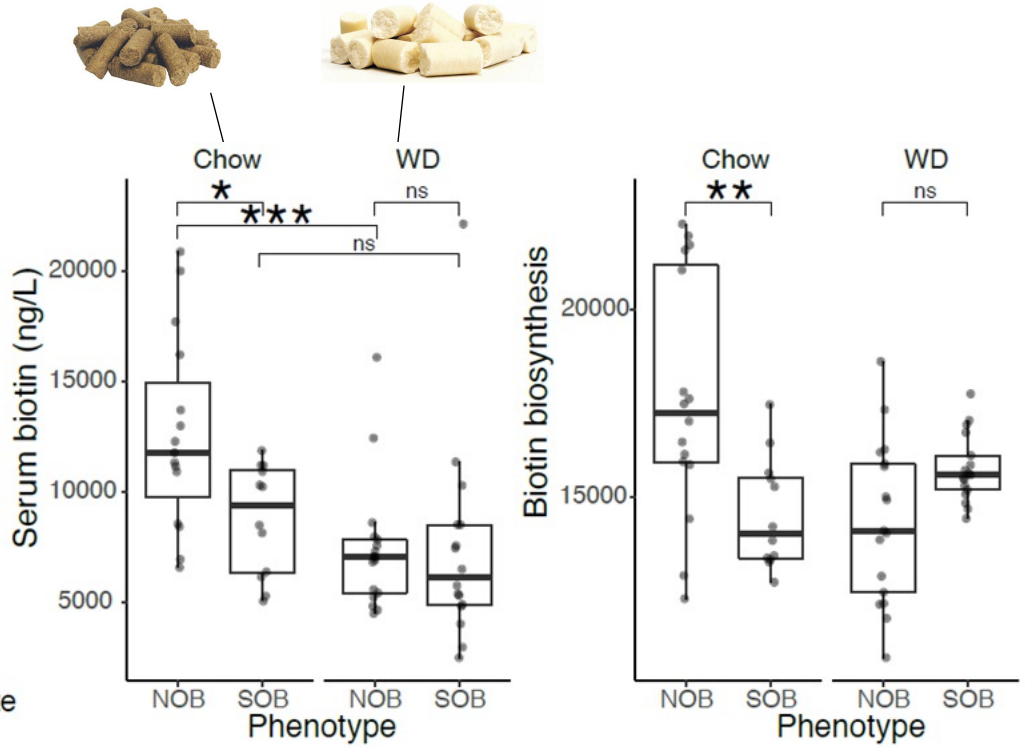
- **Decrease** of plasma biotin in Germ-free animals and mice treated with broad spectrum antibiotics

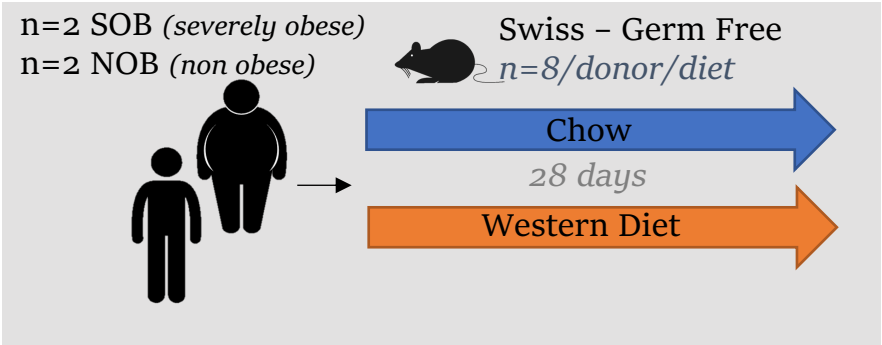
  ➔ **Part of circulating levels of biotin originates from the gut microbiota**

** p<0,05, T-test*

Fecal microbiota transfer and circulating biotin







NO donors have ↗ biotin producers

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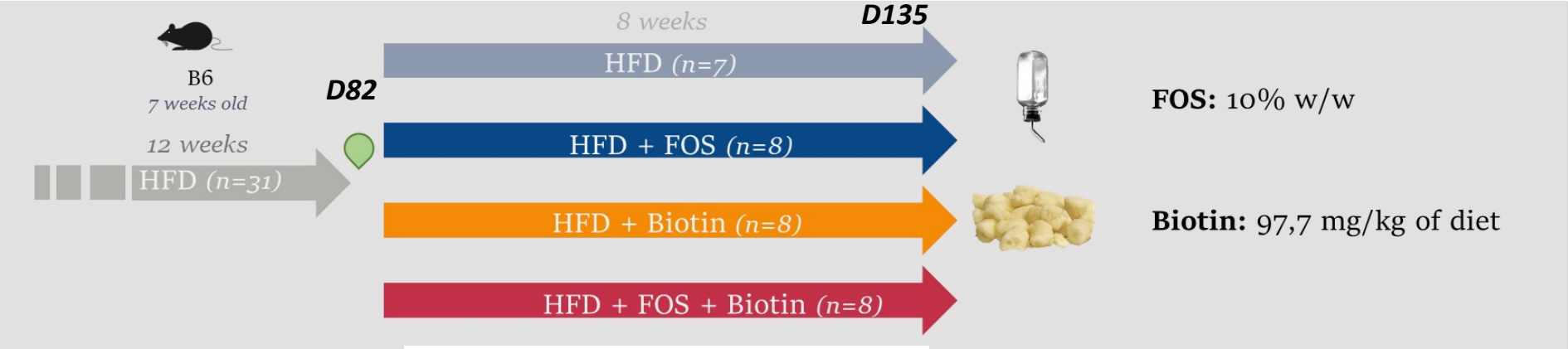
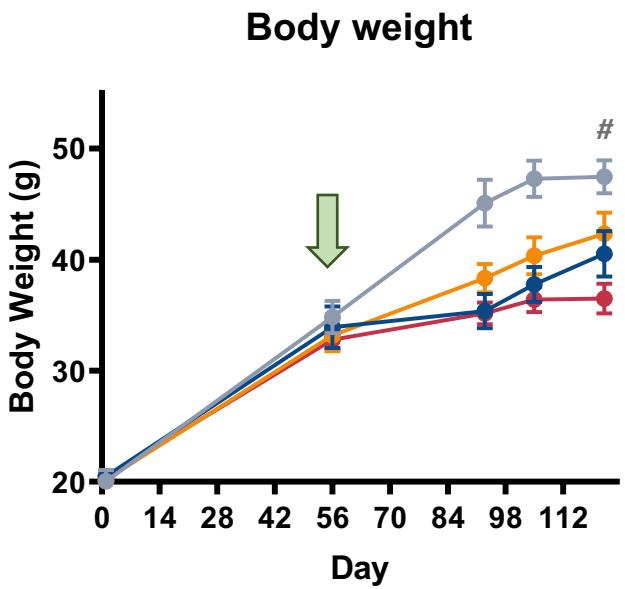
- **Diet** has an impact on biotin plasma levels **(a)**
- For chow diet: biotin level is decrease for SOB donor vs NOB donor **(b),** difference of donor's bacterial biotin production potential is transferred to mice **(c)**
- Strongest effect of the diet vs. donor for WD groups

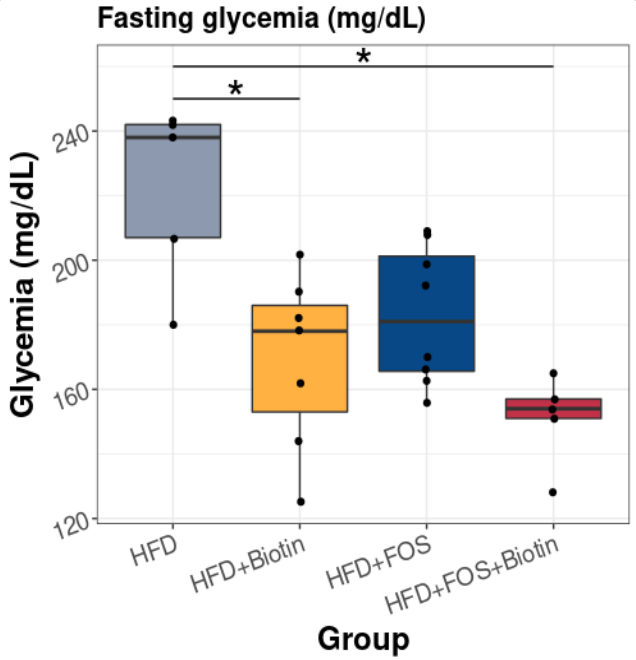
** p<0,05; ** p<0,001, T-test*

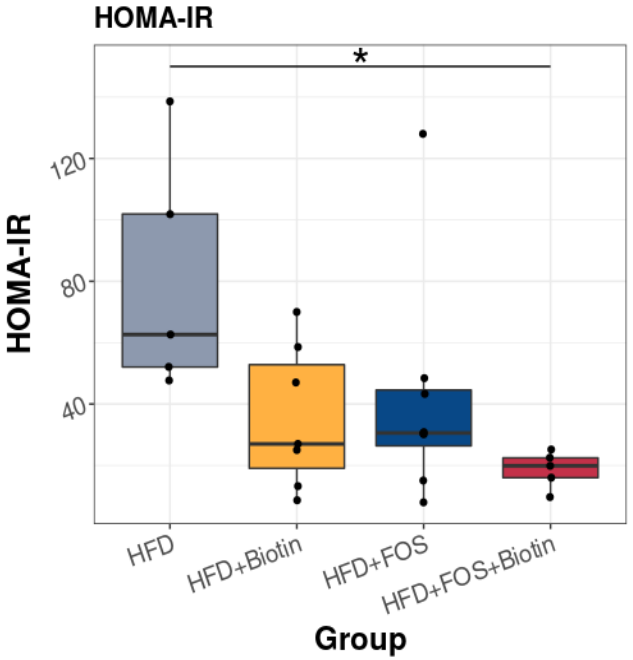
Effect of FOS + biotin supplementation in installed obesity

« Lock-down » mice





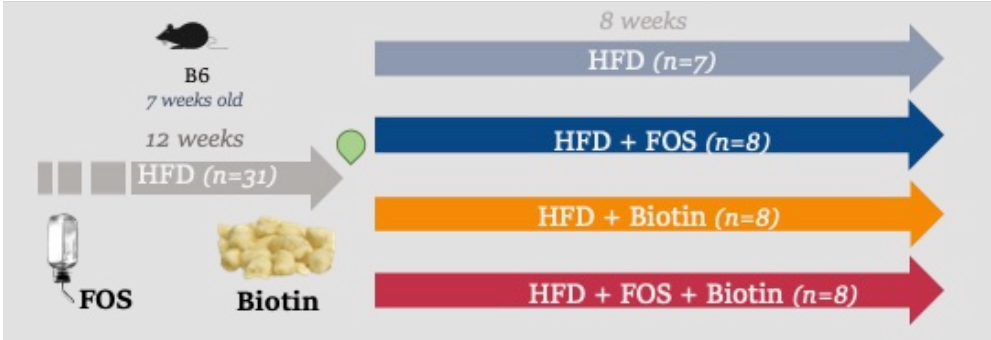


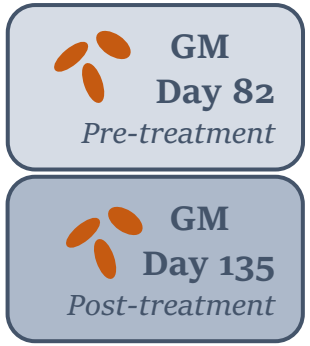


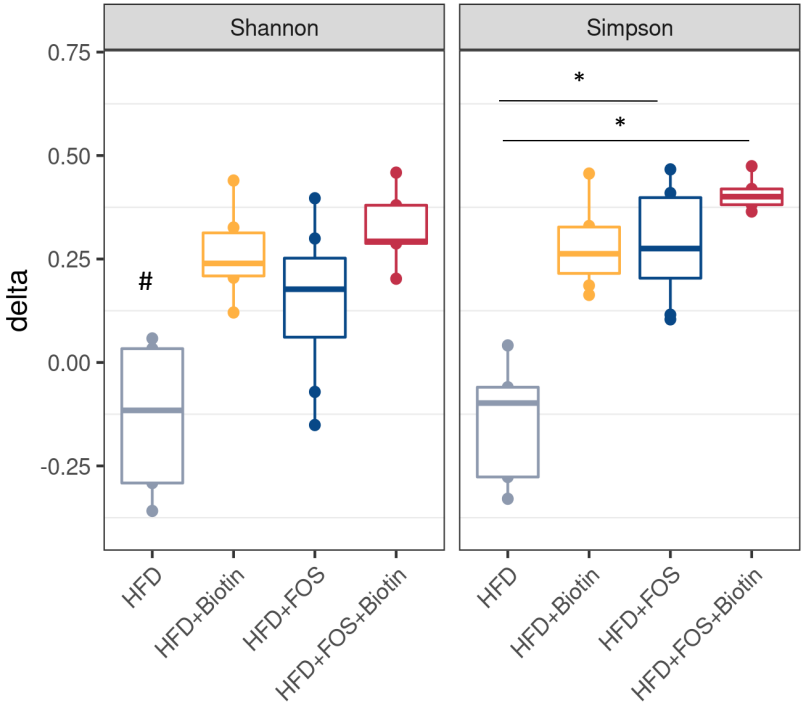
- Simultaneous supplementation of FOS + Biotin in diet-induced installed obesity **limits fat mass** (especially sub cutaneous) gain.

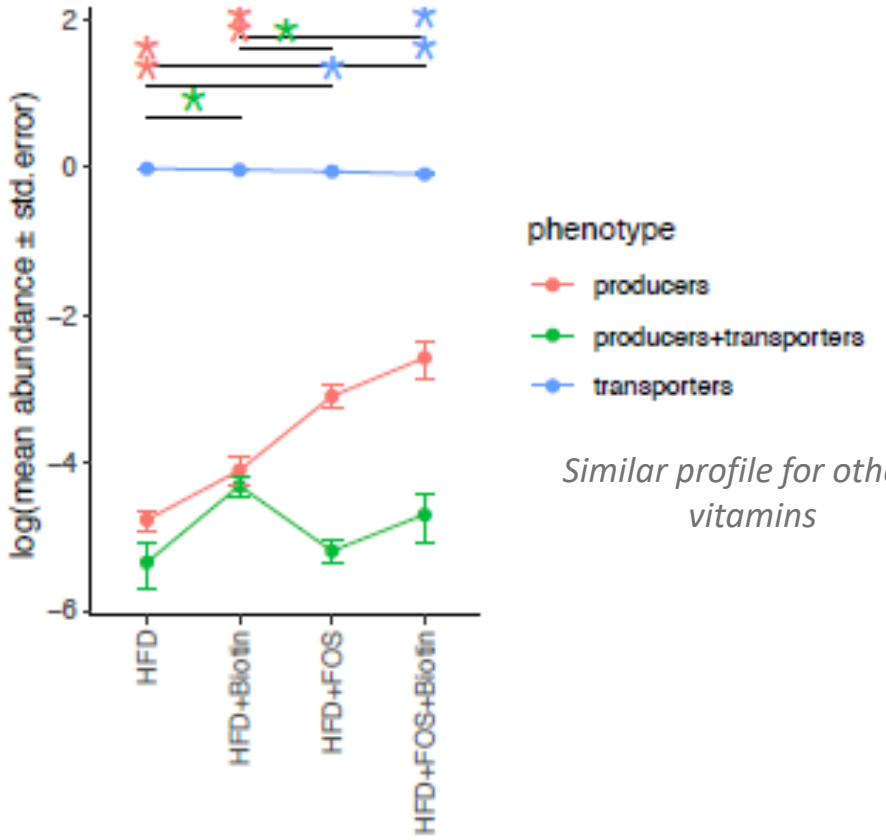
** p<0,05, ANOVA*
 # HFD vs all groups, p<0,05, ANOVA

Modulation of the gut microbiota by FOS + biotin supplementation







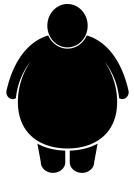


Similar profile for other B vitamins

- All treatments induce an **increase** of Shannon and Simpson indexes
- Production potential is **increased** by all treatments; abundance of bacteria harboring production & transport properties is **increased** by biotin.

**p<0.05, ANOVA*
 # HFD vs. all groups, p<0.05, ANOVA

Modulation of the gut microbiota by FOS + biotin supplementation



- Biotin bacterial metabolism
- Biotin circulating levels

Altered in severe obesity

Rescued (partly) after bariatric surgery

- Biotin bacterial metabolism
- Biotin circulating levels

Altered by absence/depletion of gut microbiota

GF

Abx

Rescued and modulated by Fecal Microbiota Transplant

Human (SOB & NOB) to mice (Chow and WD) fecal transfer

HFD

Altered by High Fat Diet feeding

Rescued after bariatric surgery

EGA

Improved by supplementation of FOS and biotin

FOS+Biotin

Importance of vitamin status consideration in severe obesity.

Perspective of prebiotic and biotin supplementation in severe obesity management

Belda*, Voland* et al Gut, 2022

nutriomics

Nutrition and obesities ; Systemic approaches

Judith Aron-Wisnewsky, **Lise Voland, Jean Débédat,, Tiphaine Le Roy, Judith Aron**, Solia Adriouch, **Pierre Bel Lassen,** Chloé Amouyal, Sébastien André, Christine Poitou, Véronique Pelloux, Rohia Alili. **Karen Assmann,** Nataliya Sokolovska…..

Jean-Daniel Zucker & Edi Eugéni Belda

UMMISCO Unité Mixte Internationale

INRA – MGP
Hervé Blottière
Nicolas Pons
Emmanuelle Le Chatelier
Florence Levenez
Joel Doré
Stanislav Dusko Ehrlich …

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Fredrik Bäckhed
Valentina Tremaroli
University of Gothenburg

Jeroen Raes
Gwen Falony
VIB

All metacardis teams !

MetaCardis

European Commission

Fondation Leducq

JPI a healthy diet for a healthy life

Fondation pour la Recherche Médicale

Agence Nationale de la Recherche ANR

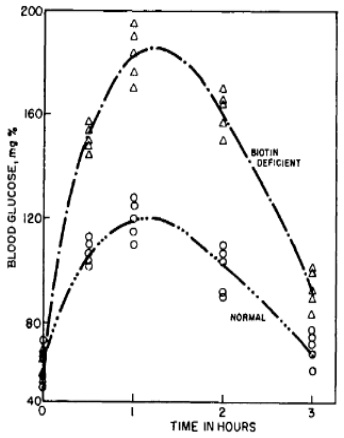
Biotin & metabolism (mice)

Literature => Deficiency

Chow diet

Dakshinamutri et al. , Experimental Biology and Medicine, 1968:

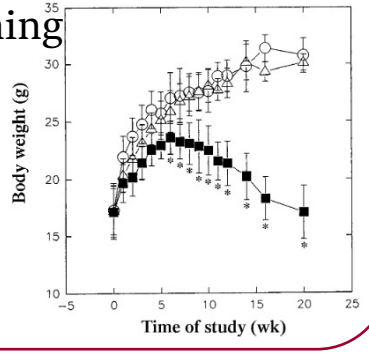
- Methods: Avidin diet (raw egg white) in rats
- Results:
  - ↗blood glucose: ↘glycogen synthesis, ↘leucin incorporation



Group	Biotin status	Glycogen mg/100 gm Liver
1	Normal	120
2	Deficient	31
3	Deficient, insulin treated	96

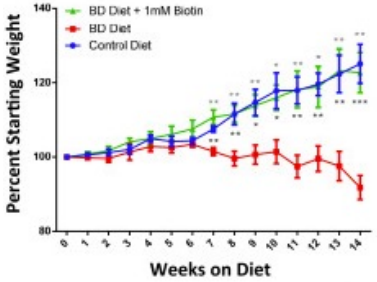
Baez Saldana et al., The American J of Clin Nutr., 1998:

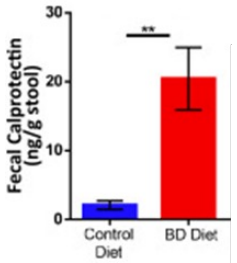
- Methods: Diet, Balb/cAnN mice, post weaning
- Results:
  - BW loss, Growth retardation
  - ↘ activity of PC, PCC in liver



Skupsky et al.,Cell Mol Gastroenterol Hepatol ,2019:

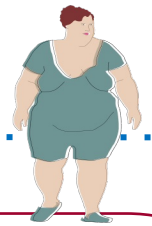
- Methods: Diet, C57BL/6J mice
- Results:
  - BW loss, alopecia,↘ activity level of the animals
  - ↗ calprotectin (inflammation marker) in feces + many features of **IBD**





Biotin **deficiency** → altered glucose metabolism & increased inflammation (under chow diet)

Biotin & Diabetes (Humans)



Literature => supplementation => 9–16 mg daily in clinical trials improves glucose metabolism

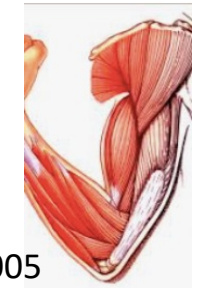
Biotin

↓

guanylate cyclase
cGMP

↑ Insulin release

↓ Glucose ouput



↑ Insulin sensitivity

Review in Mc Carthy, 2005

- ✓ **7 studies in NCT clinical trial : Biotin + Diabetes**
- ✓ RCT-double blind **Biotin** + **Chromium Picolinate**
- ✓ Geohas, 2007 => improved glucose metabolism & dyslipidemia
- ✓ Albarracin, 2007 **=> Improved metabolism and dyslipidemia in T2D+ T2D + dyslipidemic**
- ✓ => Improved glucose metabolism
- ✓ Albarracin et al, 2008 => Improved glucose control
- ✓ Revilla-Monsalve, 2006 Biotin only => triglyceride-lowering effect in T2D and non T2D

Biotin supplementation→ Improved glucose metabolism & dyslipidemia