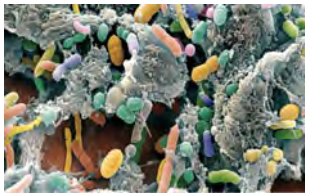
nutriOmics

Nutrition & Obesity; Systemic approaches



Eubiose et dysbiose : **où sont les signatures ?**
« le poids du microbiote dans l'obésité et le diabète »

Professeur Karine Clément MD, PhD
NutriOmics team
Inserm/ Sorbonne Université
Pitié-Salpêtrière, faculté de Medecine, ICAN

Collègue de France, 24 janvier 2017

MÉDECINE SORBONNE UNIVERSITÉ

Inserm
La science pour la santé
From science to health

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

ICAN Institute of Cardiometabolism And Nutrition

Cardio-metabolic and Nutrition-Related diseases
Heavy burden for the Society

According to WHO estimates
Non-communicable diseases (?)
Last report 2015 (WHO)

Winning trio (cause of death)

Cardiovascular diseases : 17.7 M

Cancers : 8.8 M

Pulmonary disorders: 3.9 M

Type 2 diabetes 1.6 death.

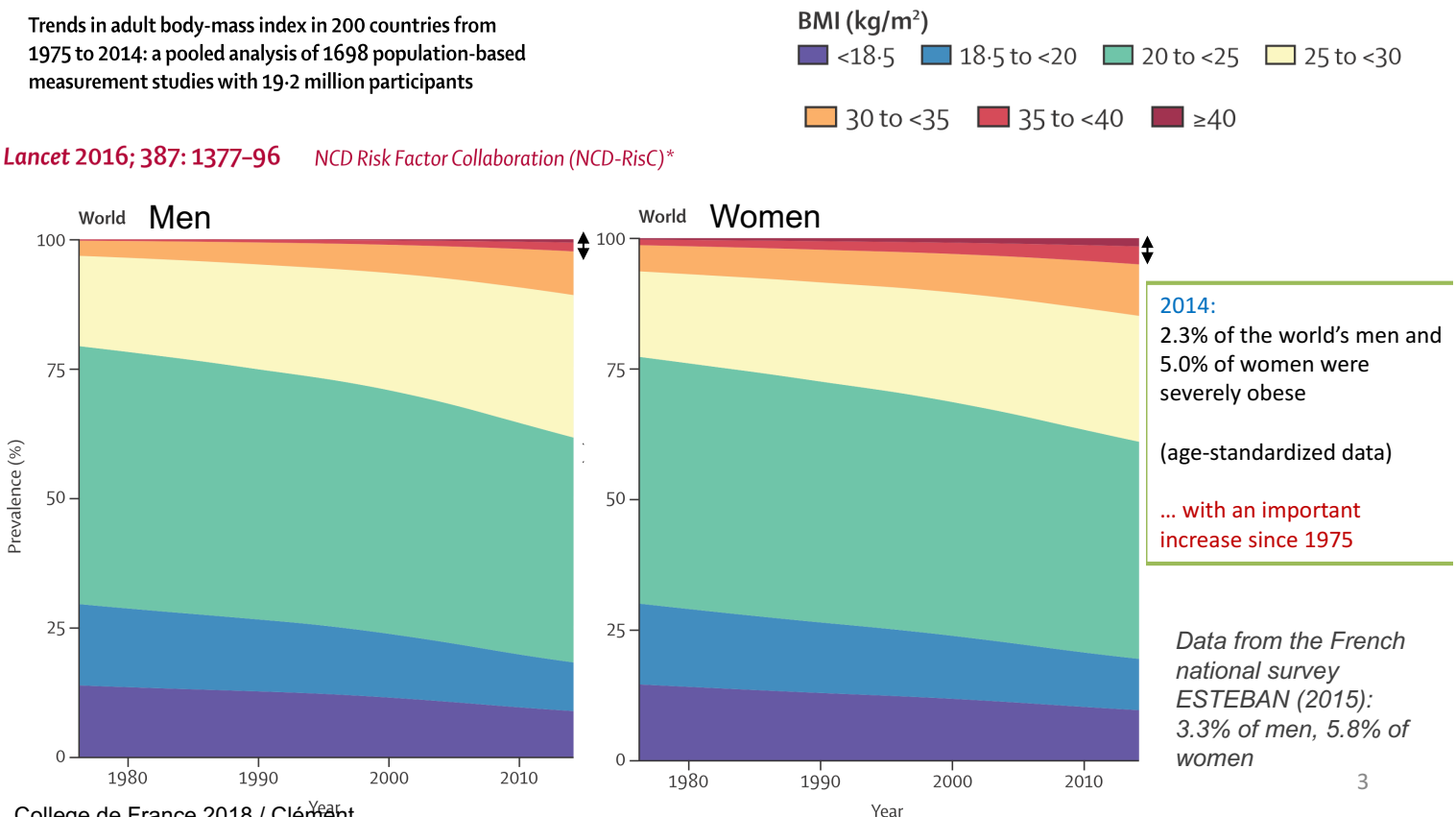
Obesity as a main contributor
Obesity is a disease (OMS 1997)

Progression of obesity?

obesity epidemiology:

Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19·2 million participants

Lancet 2016; 387: 1377–96 *NCD Risk Factor Collaboration (NCD-RisC)**



2014:
2.3% of the world's men and 5.0% of women were severely obese

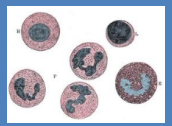
(age-standardized data)

… with an important increase since 1975

Data from the French national survey ESTEBAN (2015): 3.3% of men, 5.8% of women

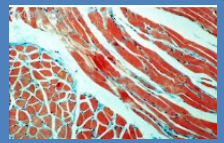
Obesities : organ & systemic disease

Lifestyle

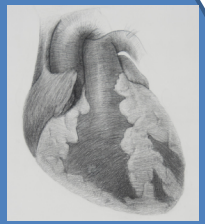


Immune system
Cytokine production

Brain
Energy balance
Endocrine function
mood



Muscle
Energy balance
Endocrine function

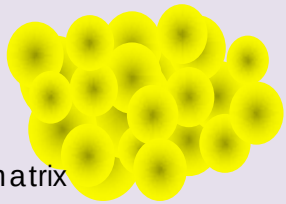


Heart injuries
Epicardial fat

Perturbed
endocrine
secretions

Immune
/inflammatory
unbalance

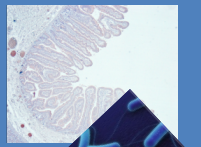
Hypertrophy

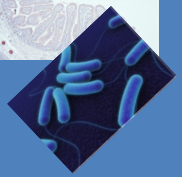


Altered
extra-cellular matrix

Altered
angiogenesis

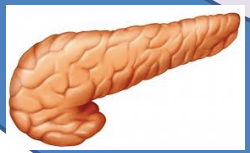
Organelle
dysfunctions





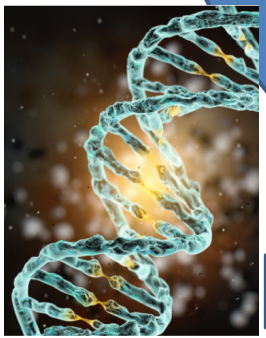
Intestine
Gut microbiota

Vascular system
atherosclerosis



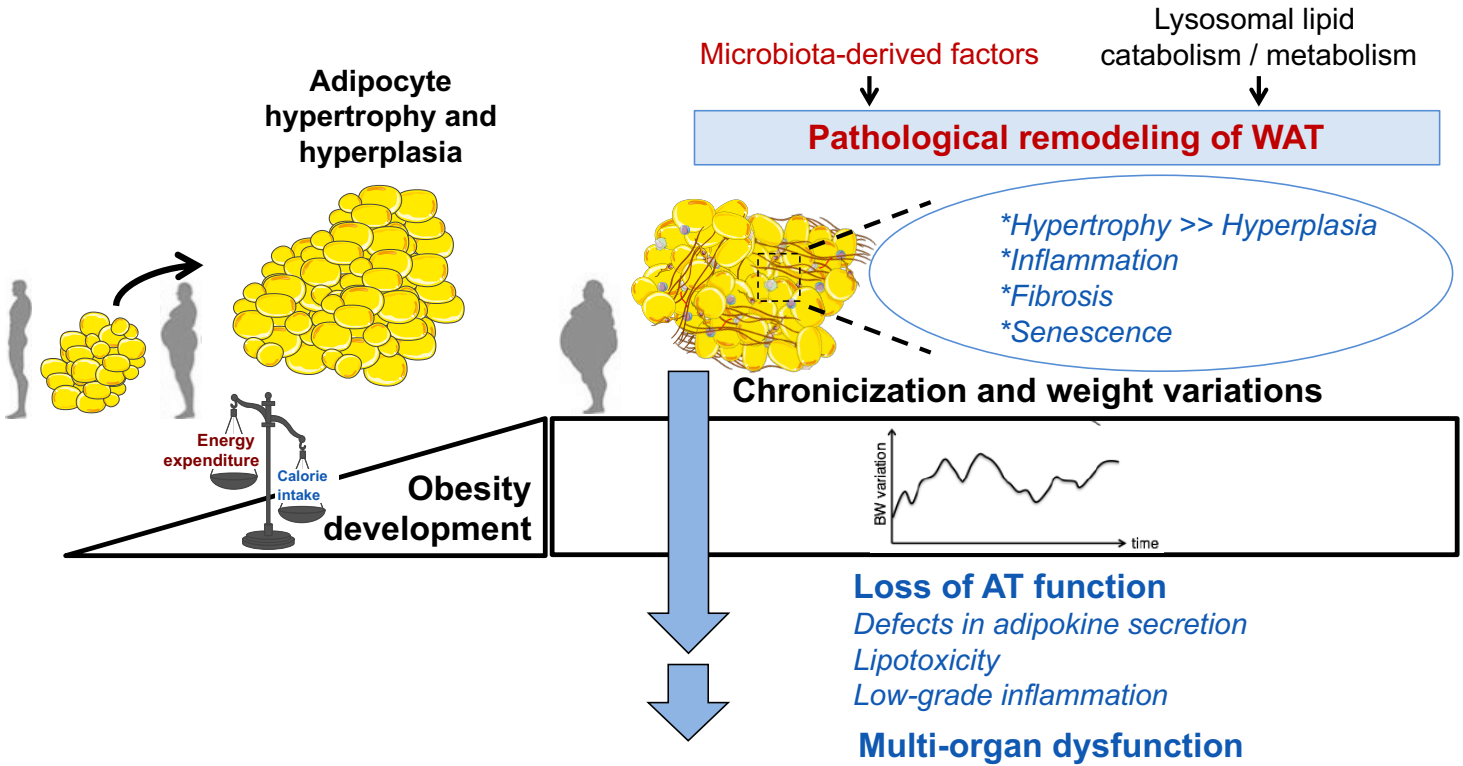
Pancreas Injuries

Liver Injuries



Genome/Epigenome/
metagenome

Adipose tissue failure is central in metabolic diseases associated with obesity

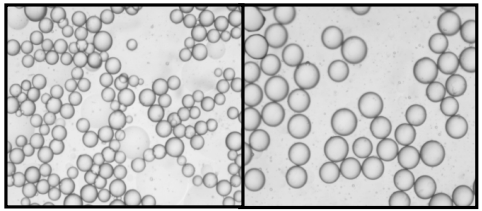


G. Marcelin

Cardiometabolic diseases
Compromised response to obesity treatment

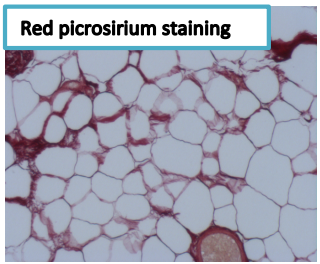
Pathological alterations of Human adipose tissue obesity

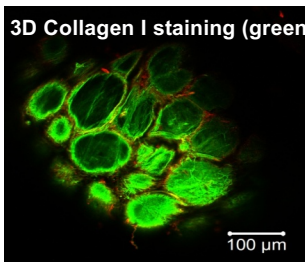
Adipocyte hypertrophia



Lean Obese

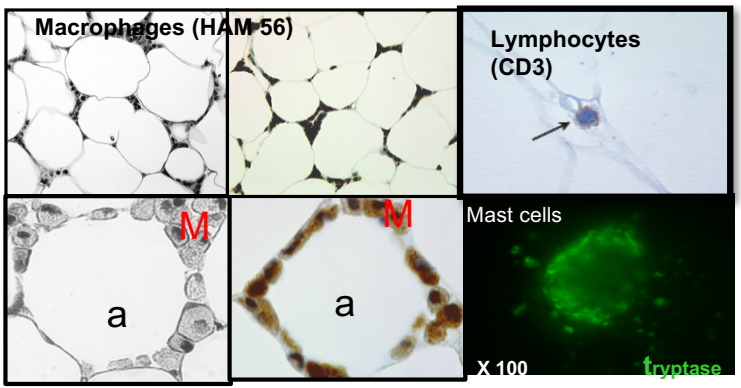
Fibrosis (pericellular)





Divoux, Diabetes 2010 *Pellegrinelli, U872*

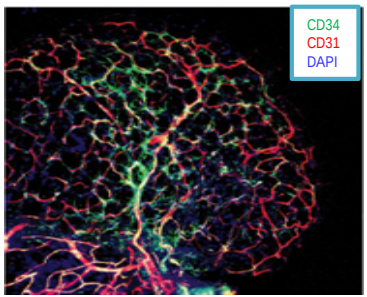
Inflammatory cell accumulation

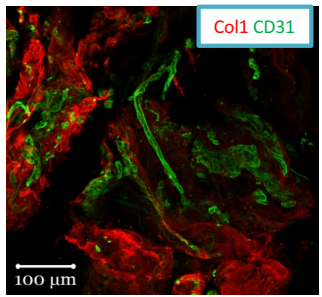


Macrophage (M) accumulation Other immune cells

Cancello, Tordjman, Diabetes 2010 U872

Vascular alterations (inflammation & senescence)

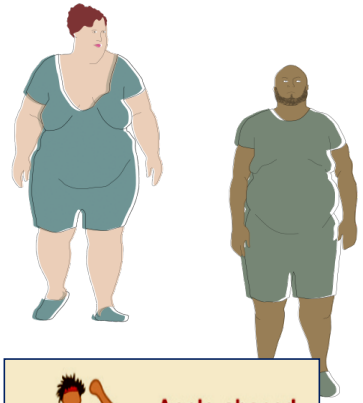




Villaret, Diabetes 2010, U *Pellegrinelli, U872*

Liu, Divoux Nature Medicine, 2009

Metabolic diseases: High phenotypic Heterogeneity



- There are many obesities (diabetes) :

⇒ *Different phenotypes in obese people living in different conditions from different genetic background involving different environmental triggers*

- Not a matter of BMI (Body fat distribution)
- Degree of severity (different disease vs. continuum?)
- Tissue & signal disease
- Different responses to treatments ?

GUT MICROBIOTA
Help in patient stratification?
Pathophysiology
Targeted treatments ?

Natural cycle of obesity development

Severe obesity

Obesity

Weight gain

Weight loss

Relapse

What are the mechanisms of fat mass expansion?

Why is it so easy to gain and so difficult to loose weight ?

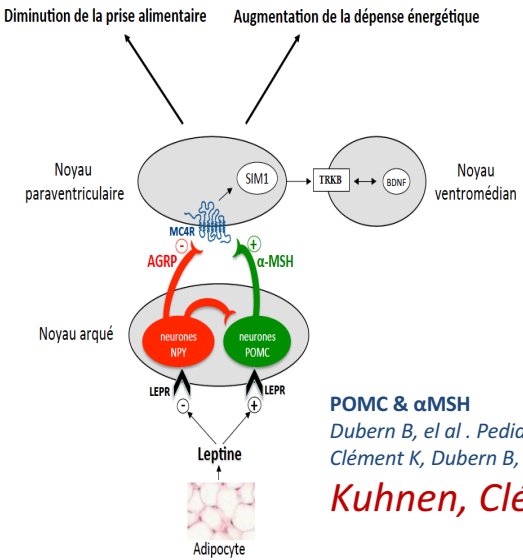
Why some obese subjects develop comorbidities

Different patients
Different clinical trajectories
Resistance to weight loss with time

Genetic obesities ; success of genetic approaches

MC4R et MC3R
Vaisse C, Clement K, Nature Genetics 1998
Dubern B, Clément K J Pediatr, 2001
Lubrano-Berthelier C, Dubern B, JCEM 2006
Dubern B, J Pediatr 2007
Roubert P, Dubern B, J Endocrinol 2010
Mencarelli, Dubern, Hum Mol Genet 2011
Valette M, Poitou C, Plos one 2012
Collet, Dubern, Mol Metabl 2017

Severe early-onset obesity
Hyperphagia
+/- endocrine /
Neurodevelopmental abnormalities



Prader-Willi Syndrome
Lloret-Linares C, IJO 2013
Coupaye M, JCEM 2013
Lacroix D, JCEM 2015
Coupaye M, 2016
Burnett LC, JCI 2017

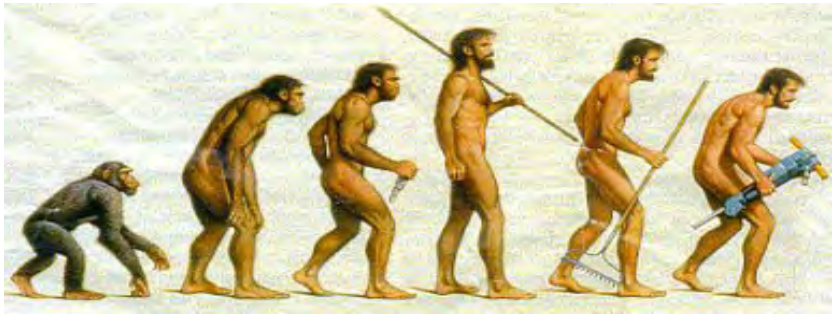
LEPR
Clément K, Nature. 1998
Lahlou N, Clement K, Diabetes. 2000
Rolland V, Clément K, Obes Res.
Le Beyec J, JCEM. 2013
Nizard, Dommergue, Clement NEJM, 2012
Huvenne H, et al, JCEM, 2015

POMC & αMSH
Dubern B, el al . Pediatr Res. 2008
Clément K, Dubern B, ET AL.. JCEM 2008.
Kuhnen, Clément et al, NEJM, 2016

New therapies (agonists MC4R)

Deep phenotypes , New genes

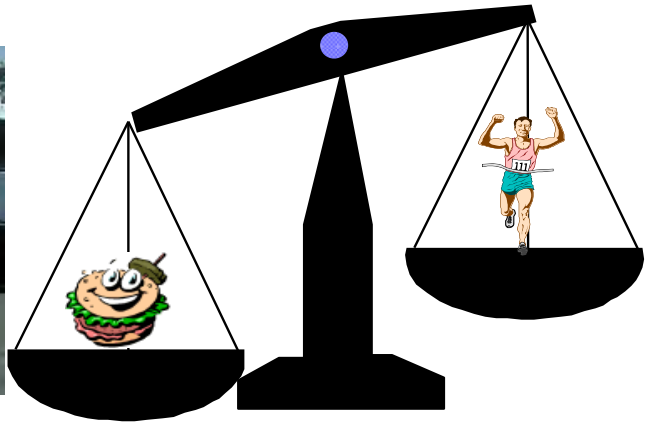
nutriomics



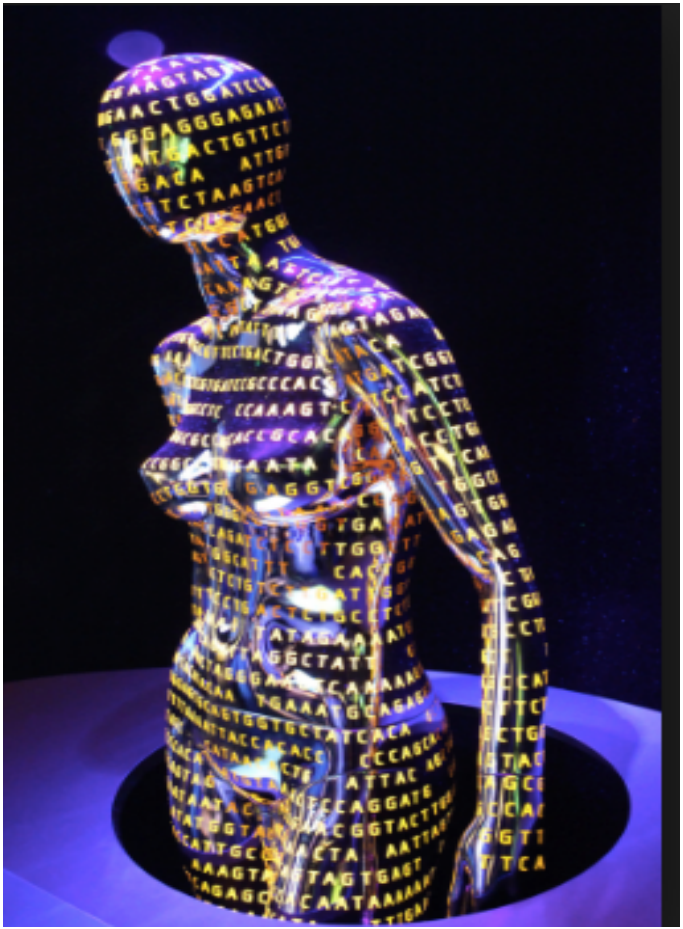
(Chronic) Obesity : disease of tissue adaptation in a context of perturbed energy balance?

Roots : can be found in gene, proteins, metabolites sensitive to variations in nutritional state

"New" Focus : the host – Gut microbiota (interaction)



Systems' biology and data integration progress



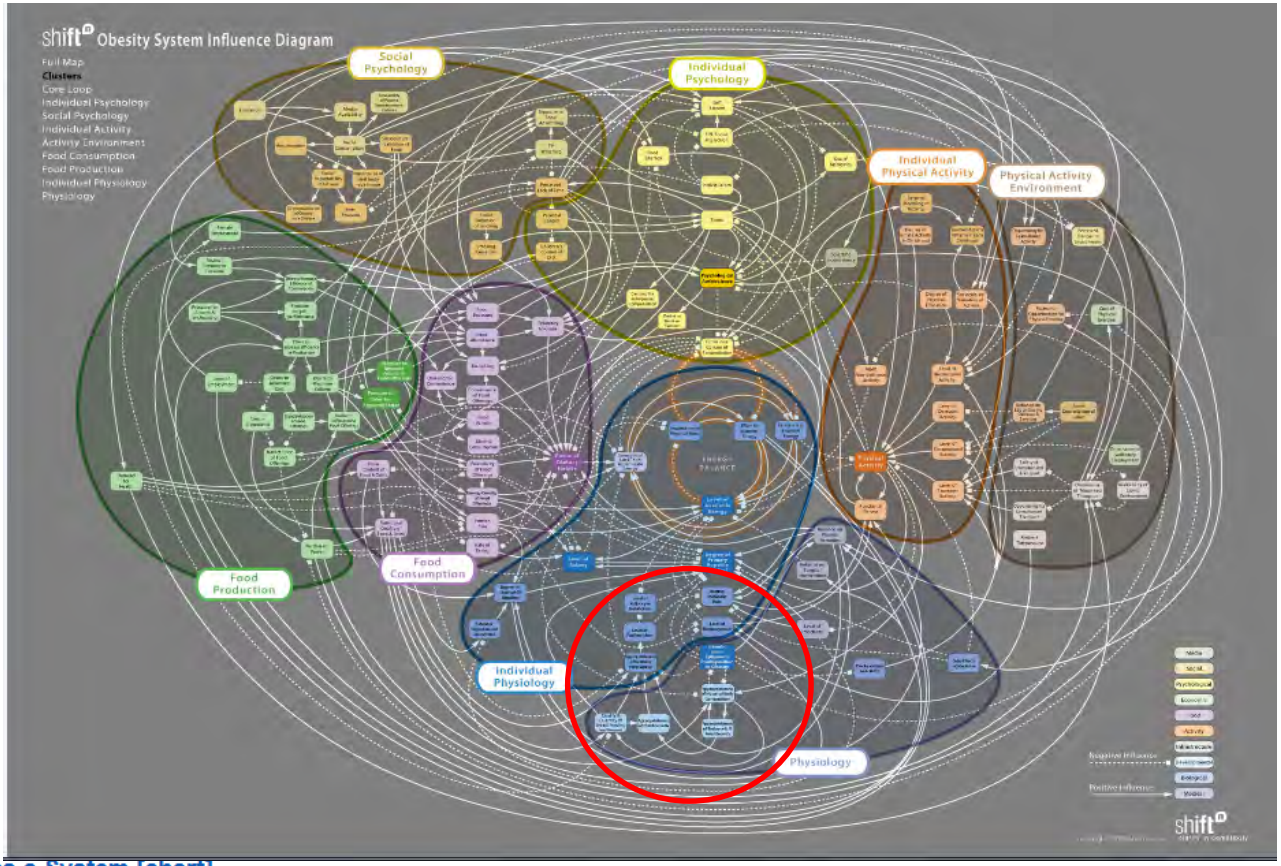
Huge amount of informations, with different orders of magnitude ?

Metaproteomics
Metagenomics
Metabolomics
Lipidomics
Functional genomics
Genomics

&
Clinical variables

=> From Model development to Application

Human obesity : example of complexity



Obesity as a System [chart]

shiftn.com — Developed for the Foresight Tackling Obesities project, this causal loop map was designed to provide systemic insight into the multiplicity of factors contributing to the obesity epidemic.

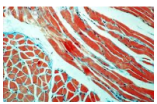
http://www.shiftn.com/obesity/zoom-map.html

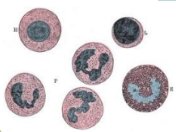
Change of society : complex disorders

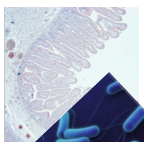
ENVIRONMENT-SOCIETY

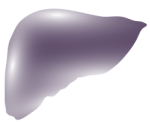
- INFECTION
- TOXIC SMOKE
- DRUGS
- URBANIZATION
- SOCIO-ECONOMICAL CONTEXT
- SEDENTARITY
- FOOD
- PSYCHOSOCIAL STRESS

GENETICS/EPIGENETICS TISSUE BIOLOGY



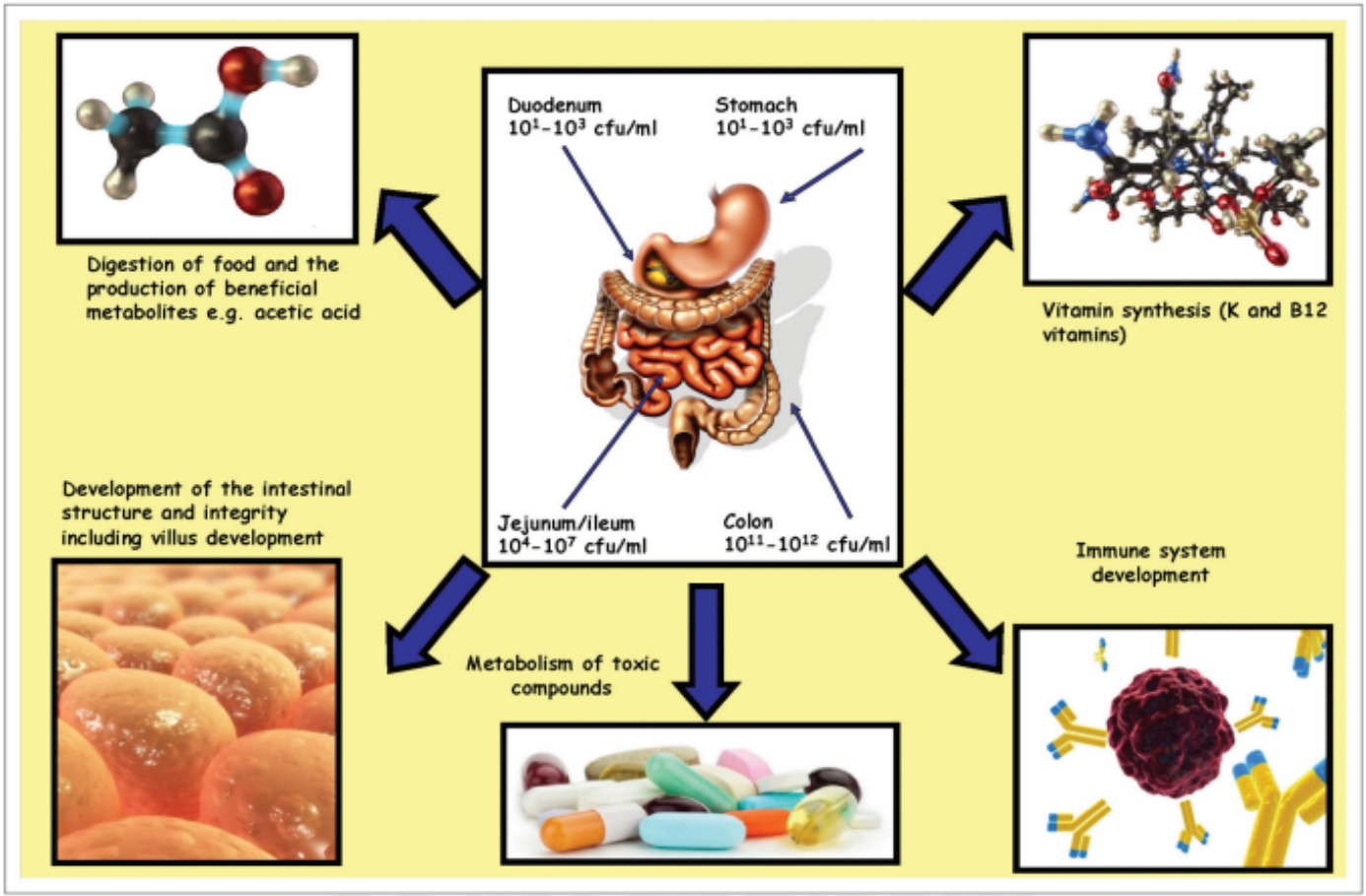






GUT MICROBIOTA MAY BE A MISSING LINK?

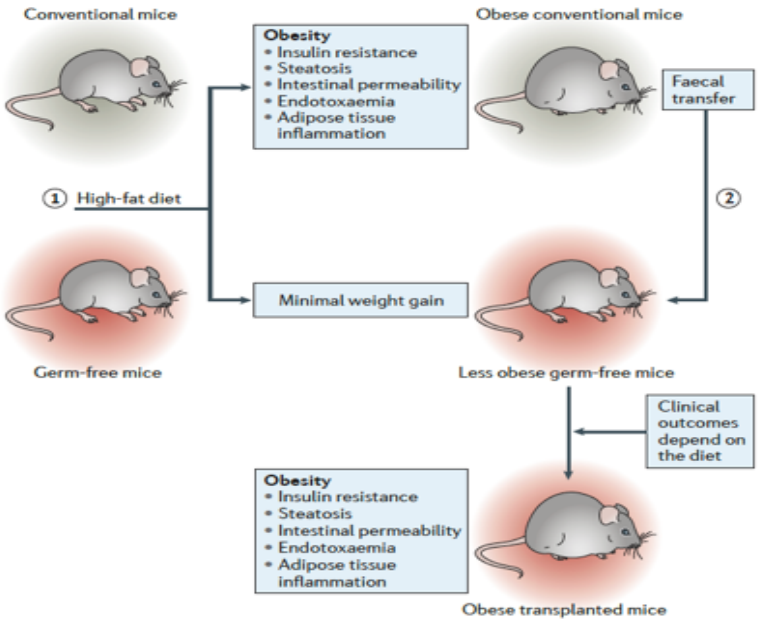
Key functions in metabolism



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

« Breakthrough findings » in mice

Mice deprived of any gut bacteria (« germ free ») have decreased adiposity, a better metabolic profile and are resistant to HFD induced weight gain



Turnbaugh et al., Nature 2006
Turnbaugh et al., Cell Host Microbe 2008
Ridaura, V. K. et al. Science 2013

Backhed et al., PNAS 2004

Aron-Wisnewsky & Clémentet al., Nature Reviews 2016

=> Obesity phenotype can be partially be transfered through gut microbiome transplantation

Microbiota in preclinical studies

REVIEW ARTICLE 2016 – FEMS Microbiology

Heterogeneity of the gut microbiome in mice: guidelines for optimizing experimental design

Debby Laukens[1,†], Brigitta M. Brinkman[2,3,†], Jeroen Raes[4,5], Martine De Vos[1] and Peter Var

Clin Transl Immunology. 2016 Jul; 5(7): e92. Published online 2016 Jul 22. doi: 10.1038/cti.2016.41 PMCID: PMC4973323

Article | OPEN

robiota/inflammation studies

Microbiota composition of simultaneously colonized mice hous gnotobiotic isolator ventilated cage regin

Randi Lundberg, Martin I. Bahl, Tine R. Licht,

Cell Host & Microbe

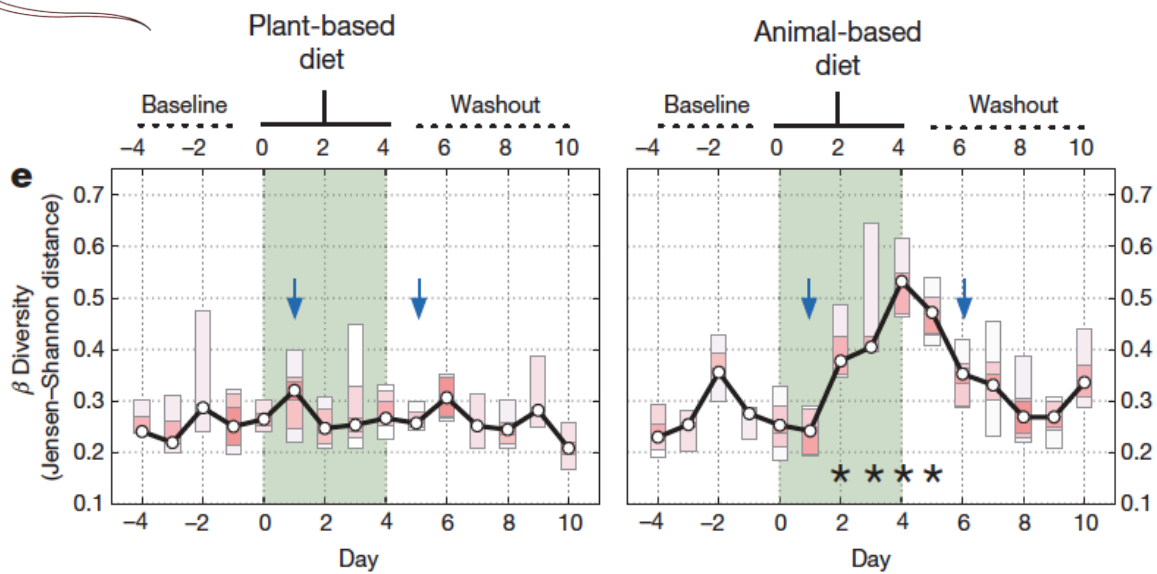
Forum

Human Microbiota-Associated Mice: A Model with Challenges

Marie-Claire Arrieta,[1,2,6] Jens Walter,[3,4,6] and B. Brett Finlay[1,2,5,*]

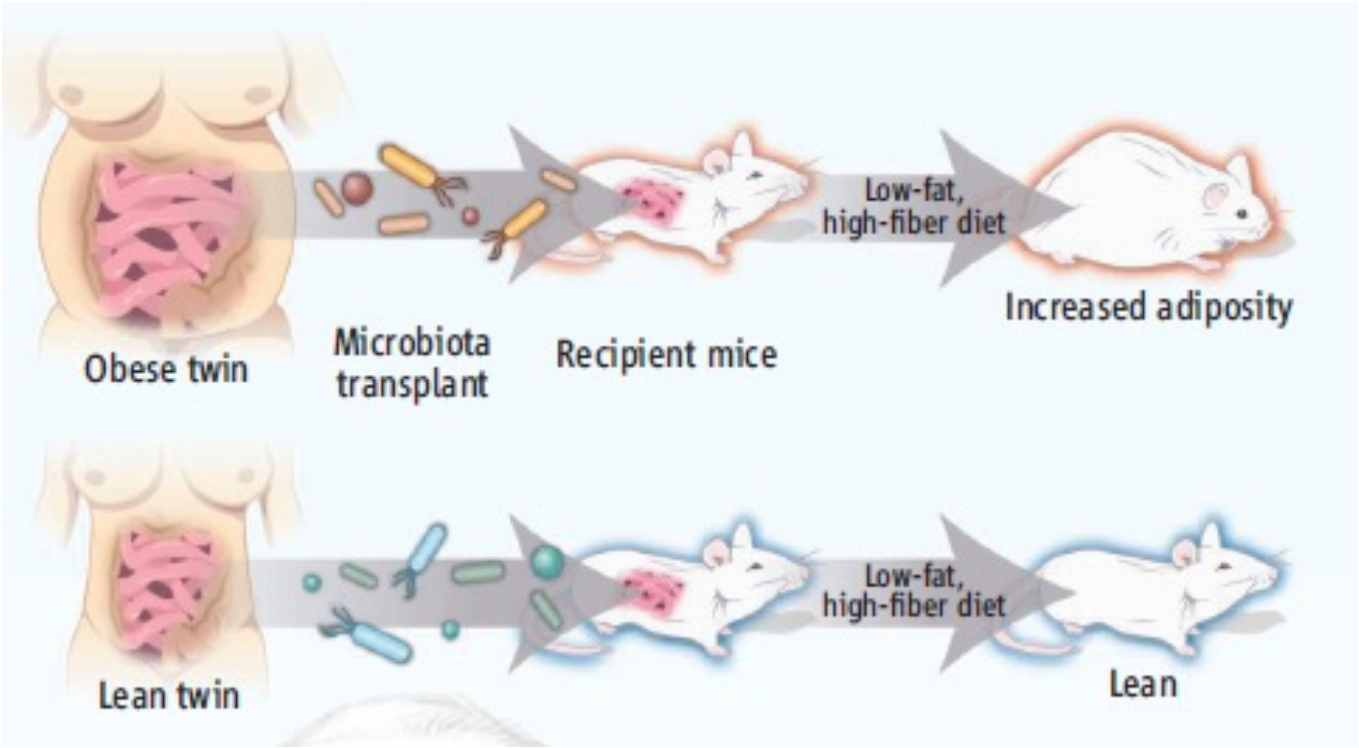
Diet matters : short term & long term

Rapid changes in microbiota composition induced by diet modification



David et al., Nature 2014

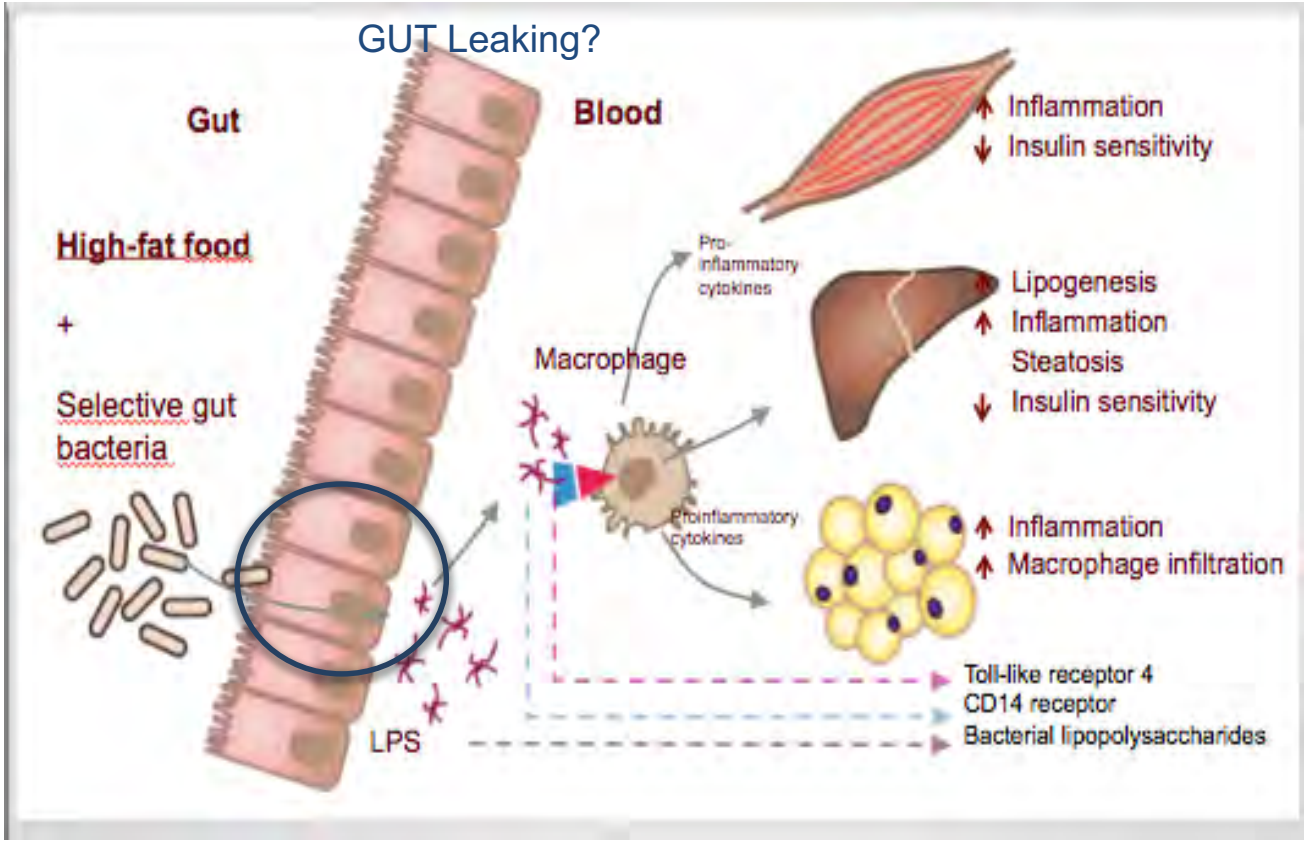
Protective role of gut microbiota from lean donnor in presence of healthy diet, Protection lost with unhealthy diet



Is obesity/diabetes a non communicable ?

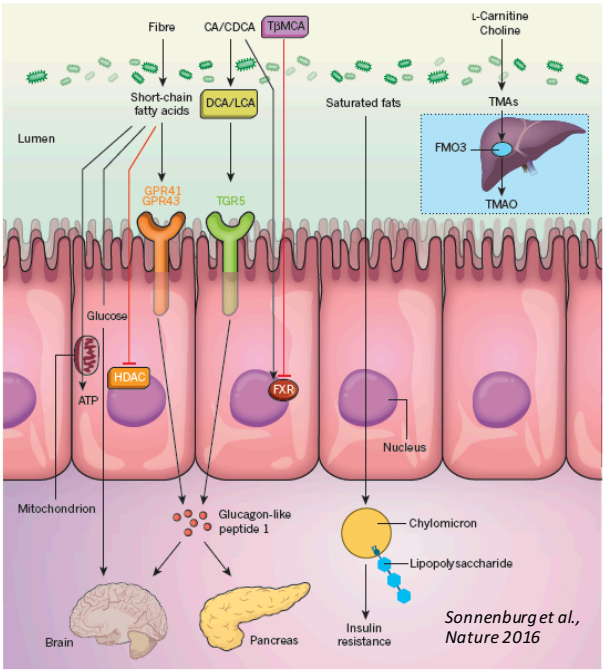
Ridaura *et al.* Science 2013; Walker and Parkhill. Science 2013

Gut Microbiota initiates insulin resistance and inflammation (Metabolic endotoxemia)



Cani P.D. et al. Diabetes 2007, Cani P.D. et al. Diabetologia 2007, Tsukumo et al. Diabetes 2007, Cani P.D. et al. Diabetes 2008, Kim et al. Circ. Res. 2007

Interaction of diet, microbiota function and host metabolism



SCFA: fermentation of dietary fiber
Insulin sensitivity, and secretion
Anti-inflammatory
Decrease food intake

Koh et al, Cell metab 2016;
Ridaura et al science 2013
Maslowski et al., Nature 2009
De Vadder et al., Cell Metab 2014
Chambers et al., Gut 2015

Secondary bile acids
Insulin secretion

Sayin et al., Gut 2013
Li et al., Nature Comm 2013
Jiang et al., JCI 2015
Wahlström et al., Cell metab 2016

Branched chain amino-acids (BCAA) produced by « LGC » microbiota
Associated with insulin resistance

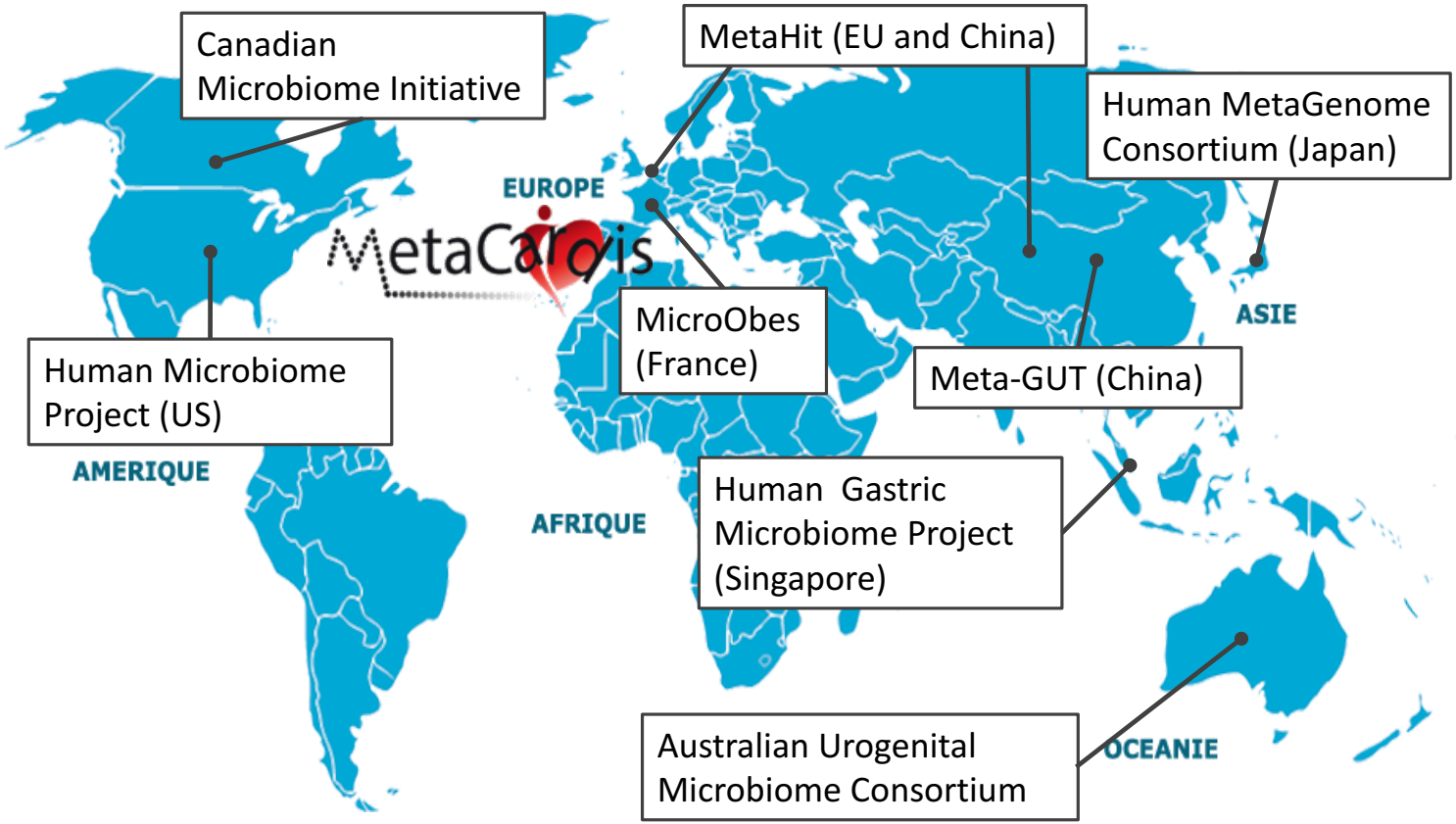
Wang et al., Nat Med 2011
Lee et al., Diabetes Care 2016
Pedersen, et al., Nature 2016

TMAO
from bacterial metabolism of cholin and L-carnitin
Associated with cardiovascular risk

Tang, et al NEJM
Wang et al., Nature 2011
Koeth et al., Nature Med 2013
Wu et al. Gut 2016

Gut microbiota derived metabolites from diet may play a key role in the regulation of host metabolism

Human Metagenomics

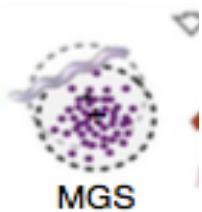


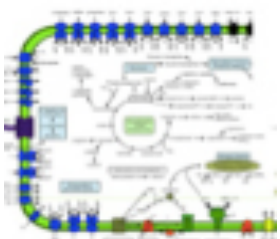
Shot Gun analysis

Clinical models

Deep phenotyping

Subject	A	B	C	D	E
Gene 1	1	1	1	0	1
Gene 2	0	0	0	1	0
...	1	1	0	1	0
Gene 3.9M	0	0	1	1	1
Total	50K	20K	40K	60K	70K





Sequencing (shot gun)
New developments
(Nanopore)

Build metagenomic species (MGS) (gene catalogue)

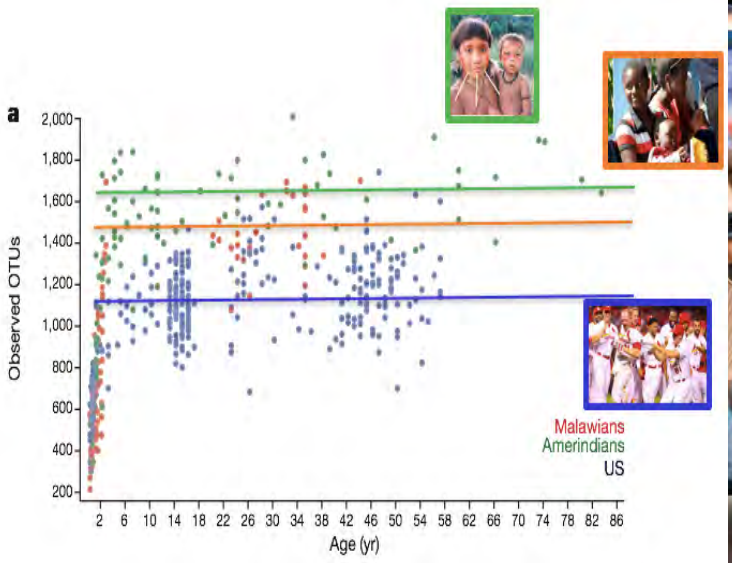
Nielsen *et al*. Nature Biotechnology 2014

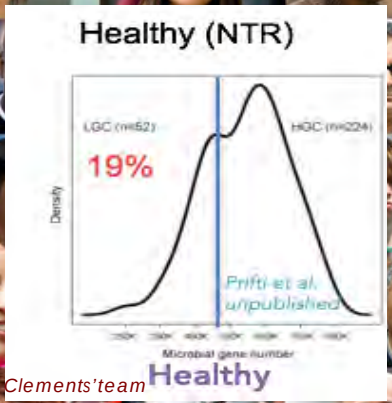
Metabolic reconstruction

Other “omics” metabolomics

=> Data integration

Yatsunenko et al, Nature 2012

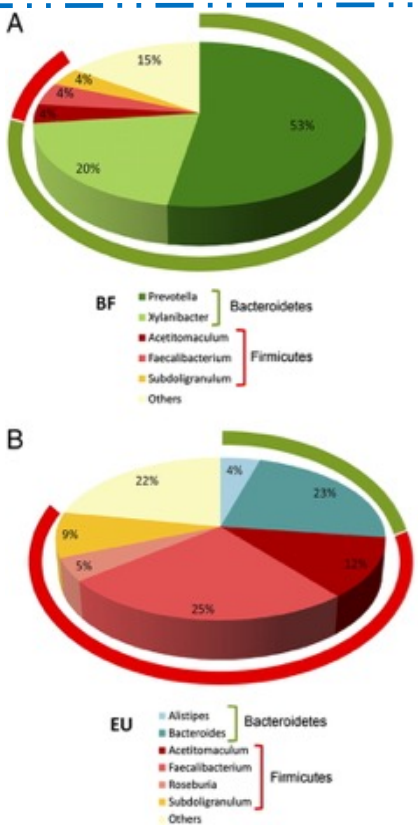




Clements'team

Diversity matters

Ethnicity on microbiota & food composition matters



Carlotta De Filippo et al. PNAS 2010

Children from Burkinafaso

High fiber and carbohydrate diet

More prevotella

*"The average amount of fiber in BF diet is **10.0 g/d (2.26%)** in 1- to 2-y-old children and **14.2 g/d (3.19%)** in 2- to 6-y-old children"*

Children from Europe

High fat and protein diet

Bacteroides

*The fiber average content in EU diet is **5.6 g/d (0.67%)** in 1- to 2-y-old children and **8.4 g/d (0.9%)** in 2- to 6-y-old children*

ARTICLE Nature May 2011

doi:10.1038/nature09944

Enterotypes of the human gut microbiome

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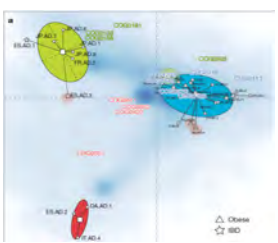
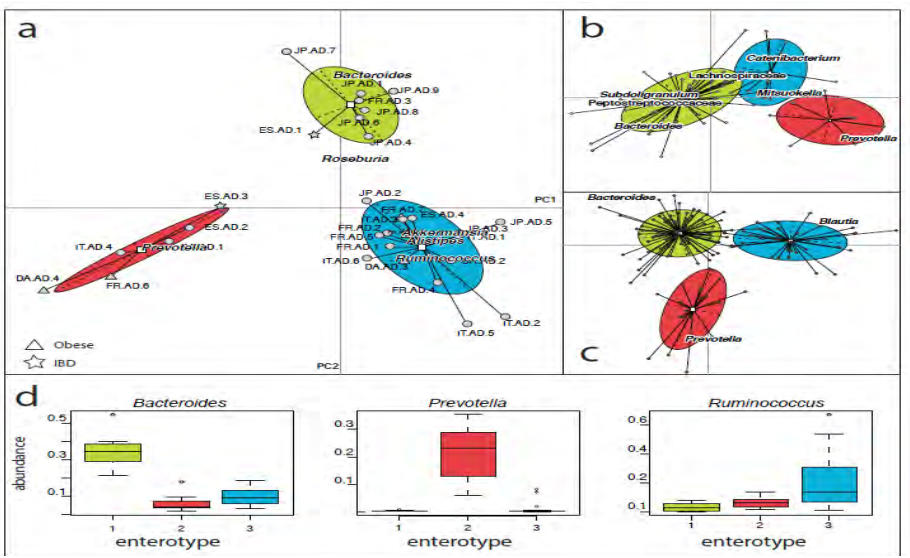
Europeans, Americans, Asians. n=33; Sanger



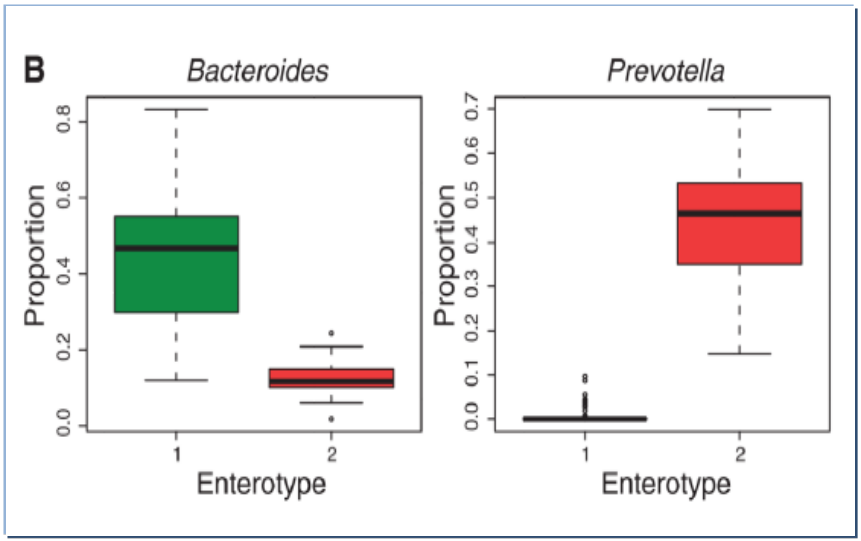
Function, n=33



Danes n=85; Illumina

US n=154; 454

Human Gut Microbiome: 3 enterotypes associate with Food intake patterns (FFQ)



Animal Fat

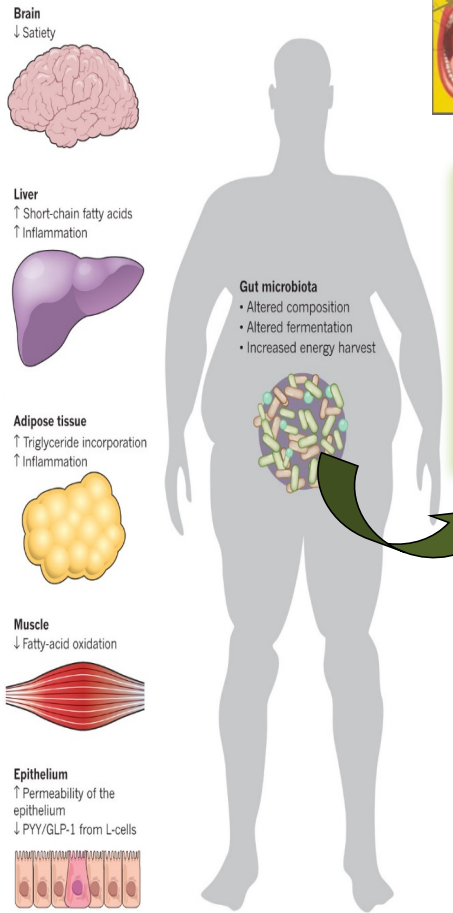
Carbohydrates

• ***Bacteroides*** **enterotype 1** associates with a diet enriched in protein and animal fat as estimated from food frequency questionnaire

•***Prevotella*** **enterotype 2** associates with a carbohydrate-enriched diet

Wu et al science 2011

Main concepts



Buccal microbiota (Koren O et al. PNAS. 2011 or Hyvärinen K et al. 2012, Atherosclerosis, 2012

Gut microbiota Composition:

Gene richness

Specific species or bacterial groups

Bacterial Metabolites *(i.e. SCFA, TMA, TMA0)*

Bacterial Components *(i.e. LPS) Others*

Energy harvest, lipid metabolism, markers for increased risk of chronic disease (CVD, T2D)

Brown & Hazen, Ann Rev med 2015

Innate immunity stimulation

Inflammation

Insulin resistance

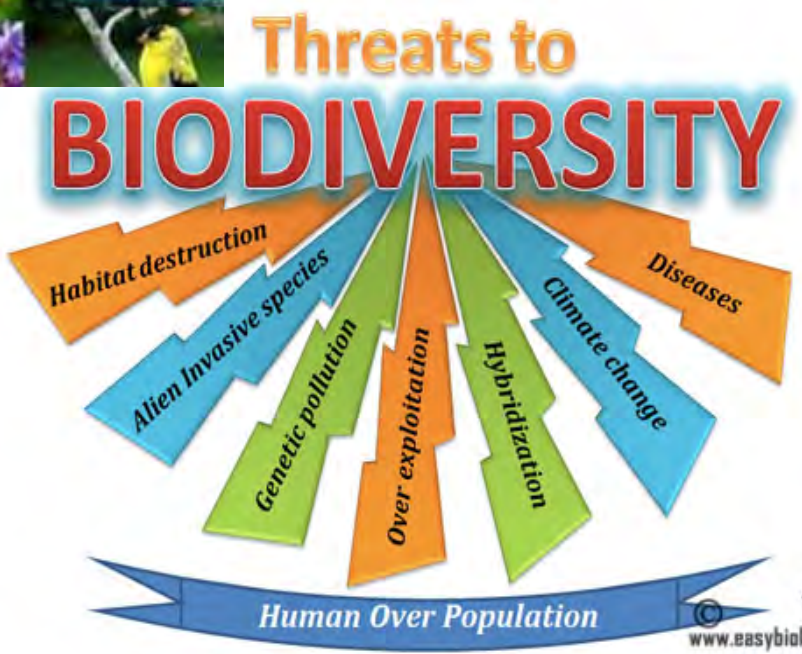
Metabolic syndrome

Chronic disease (CVD, T2D)

Tremaroli *et al.* Nature 2012

Adapted from Harris *et al.* J Obes 2012

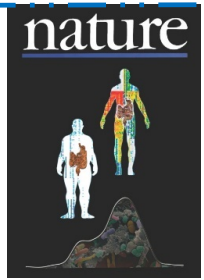
Biological
+
Diversity
=
Biodiversity



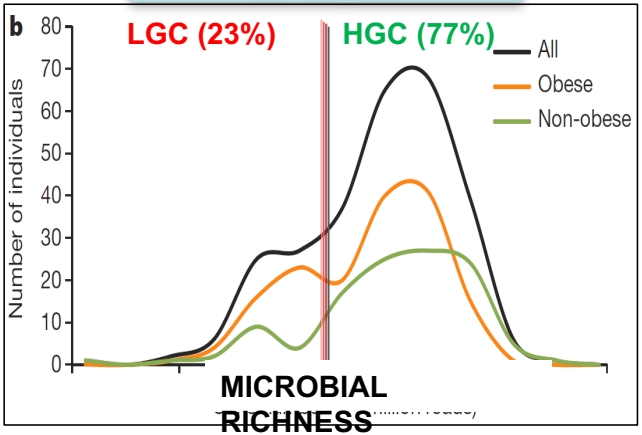
Impact on metabolic Health ?

Microbial richness : A phenotype ?

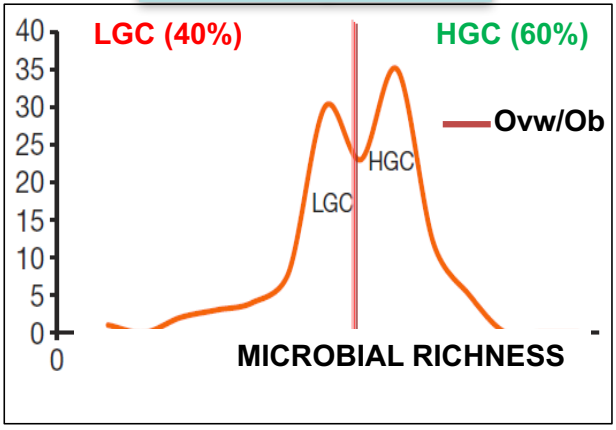
Diversity



METAHIT
292 subjects



MicroObes
49 subjects



LGC = Low gene count

HGC = High gene count

LGC: ↗ Pro-inflammatory
- *Cl. bolteae*
- *Cl. symbiosum*
- *Cl. clostridioforme*
- *Cl. ramosum*
- *R. gnavus*

HGC: ↗ Anti-inflammatory
- *F. prausnitzii*
- *R. inulinivorans*
- *Co. eutactus*
- *M. smithii*

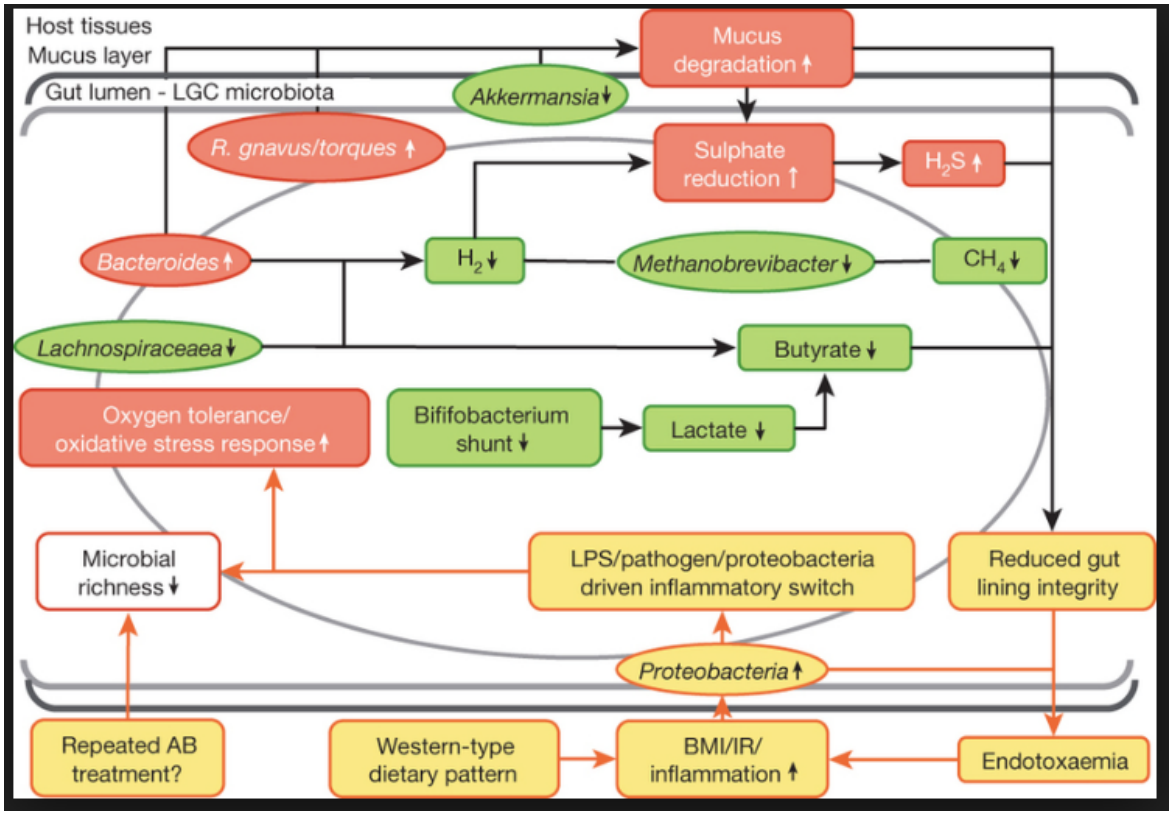
And healthier diet

LGC associates with CMD risks

- ↑↑ dyslipidemia
- ↑ adiposity
- ↑ insulin resistance
- ↑ inflammation (circulating and adipose tissue)

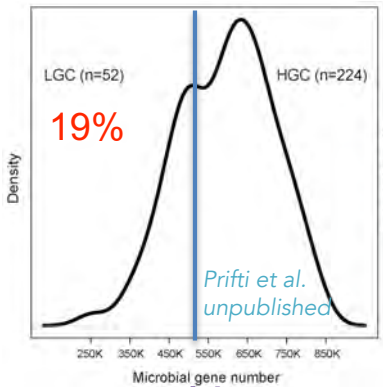
Le Chatelier *et al.* Nature 2013
Cotillard *et al.* Nature 2013
Kong & Holmes *et al.* PLoS ONE, 2015

Low richness has functional consequences



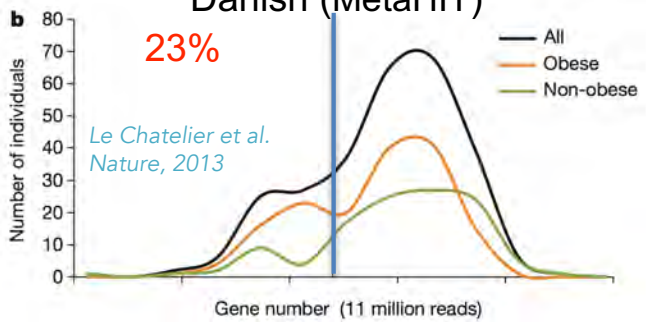
Le Chatelier *et al.* Nature 2013

Healthy (NTR)



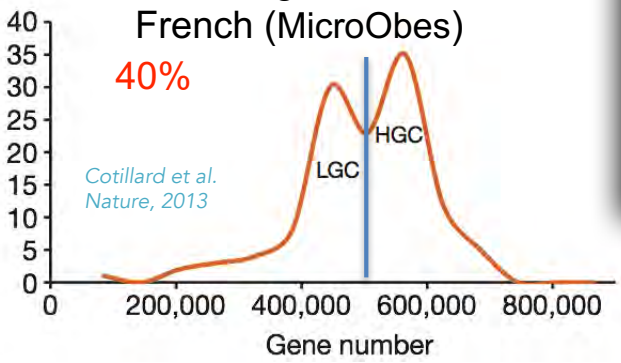
Healthy

Overweight/obese
Danish (MetaHIT)



healthy & obese

Overweight/obese
French (MicroObes)



overweight & obese

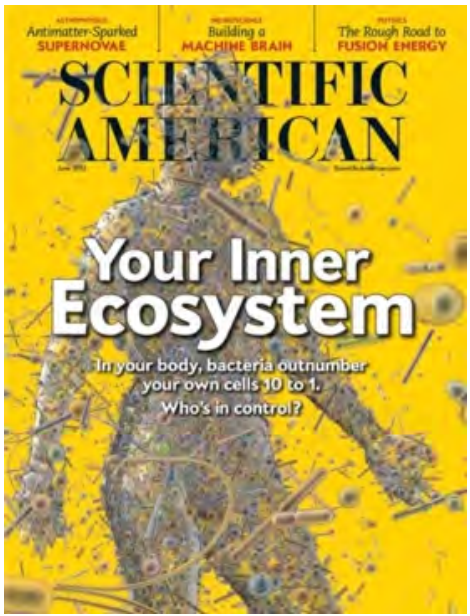
LGC prevalence increases with obesity severity

nutriomics

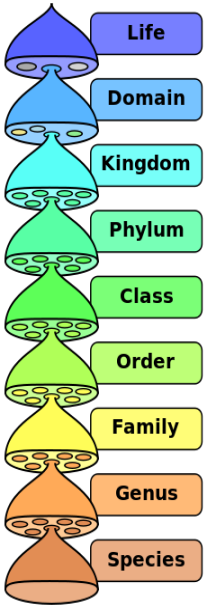
Loss of richness & ecosystem
Is Akkermansia Muciniphila a candidate to improve metabolic health ?

Better Focus on ecosystem rather than one species?

Too follows…



Diversity & "beneficial" bacteria : Akkermansia muciniphila (Akk)



Bacteria

Verrucomicrobia

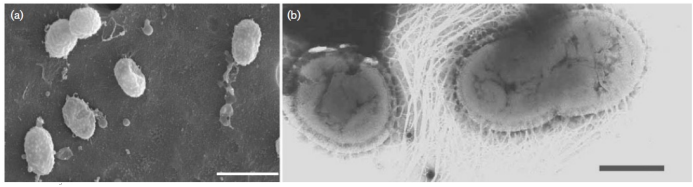
Verrucomicrobiae

Verrucomicrobiales

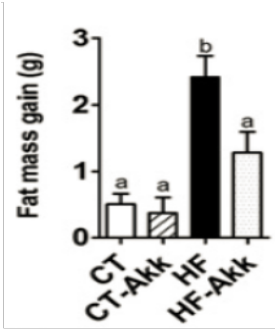
Verrucomicrobiaceae

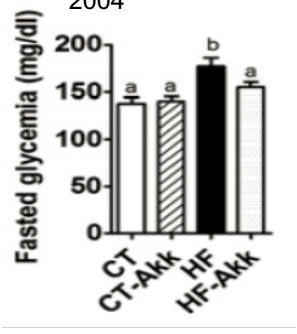
Akkermansia

Akkermansia muciniphila



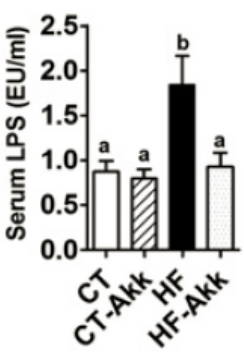
Derrien *et al.* IJSEM 2004

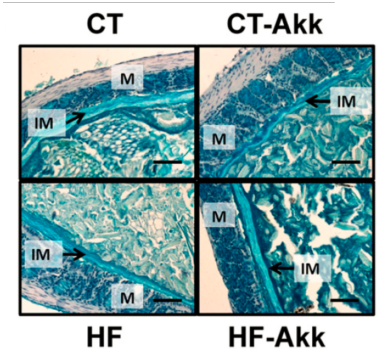




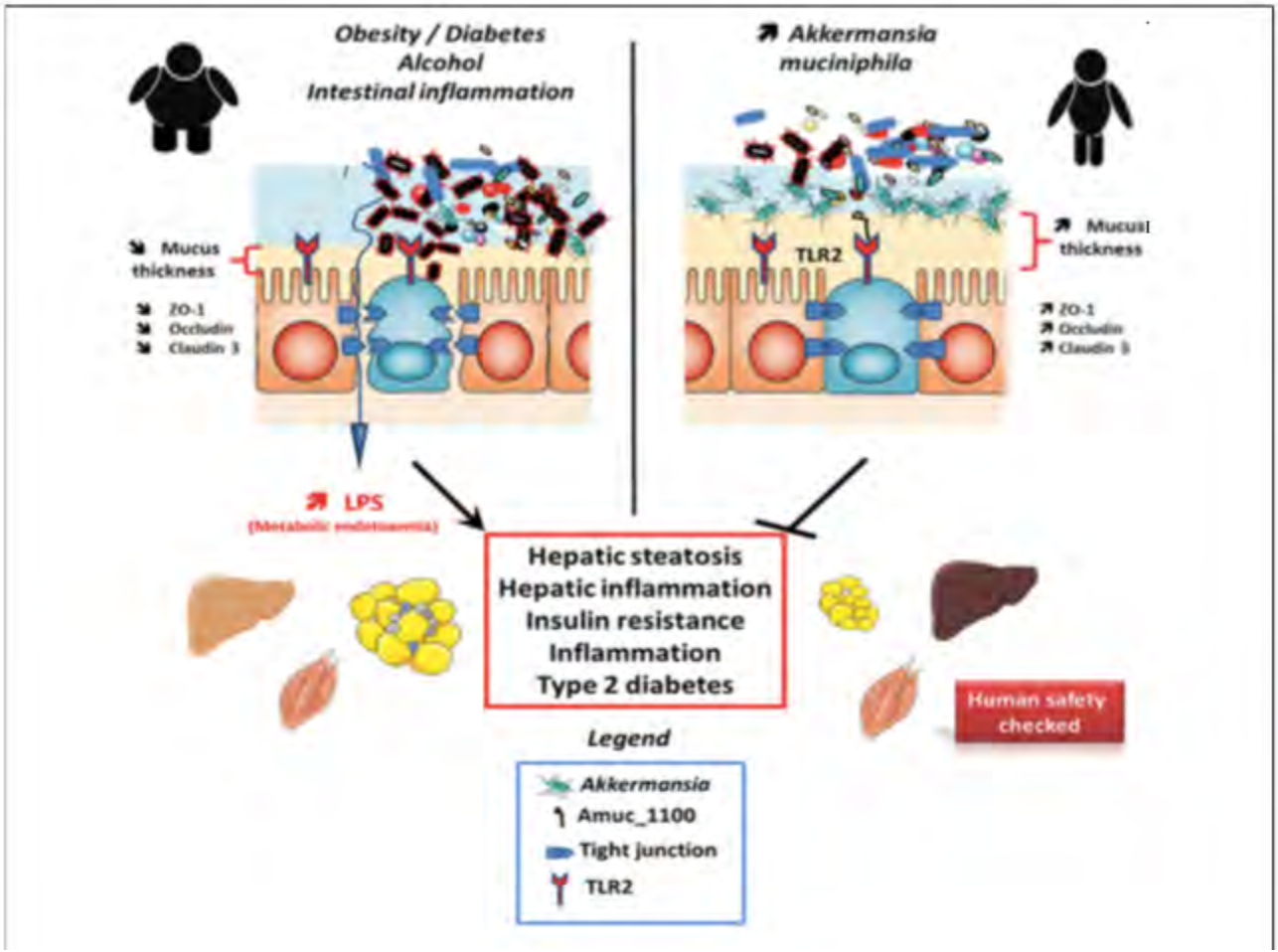
Health implications

- **Mouse studies: maintenance of glucose homeostasis.** *Everard et al. PNAS 2013*
- **Links with Metformin.** *Shin et al. Gut 2013*
- **Membrane Protein (Amuc_1100); recap effect of Akk (Plovier H, Nature Med, 2017)**





Everard *et al.*, 2013, PNAS


Obesity / Diabetes
Alcohol
Intestinal inflammation
Akkermansia muciniphila
Mucus thickness
ZO-1
Occludin
Claudin 3
TLR2
Mucus thickness
ZO-1
Occludin
Claudin 3
LPS
Hepatic steatosis
Hepatic inflammation
Insulin resistance
Inflammation
Type 2 diabetes
Human safety checked
Legend
Akkermansia
Amuc_1100
Tight junction
TLR2

P. Cani

Higher baseline *A. muciniphila* is associated with a healthier metabolic status, and more insulin sensitivity

Dao *et al.* Gut 2015

Subjects with higher *A. muciniphila* abundance and microbial richness have healthier metabolic profile

Carlota Dao

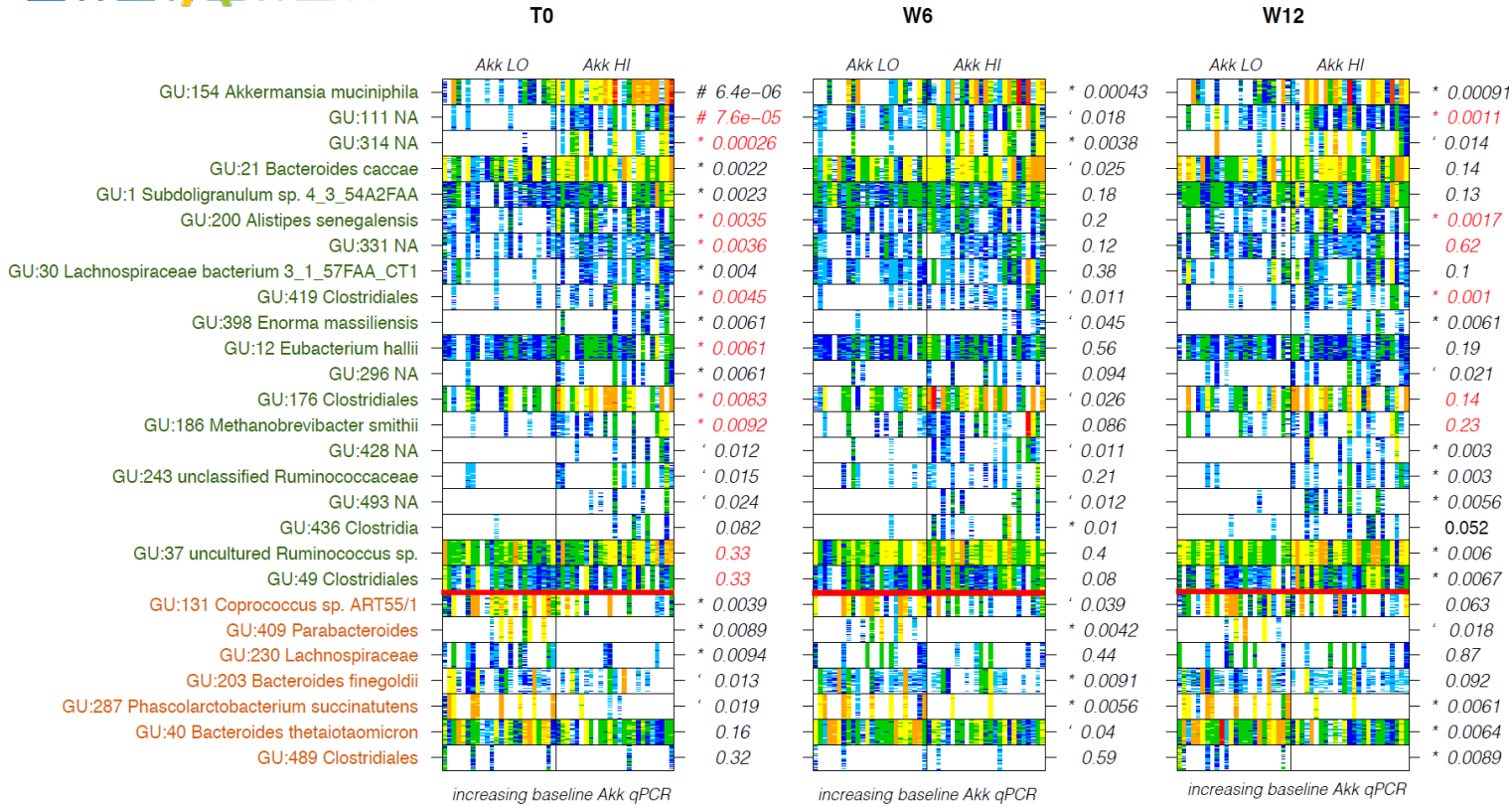
- Akk LO, LGC (N = 9)
- Akk HI, LGC (N = 9)
- Akk LO, HGC (N = 11)
- Akk HI, HGC (N = 16)

*p<0.05, **p<0.01; Kruskal-Wallis, Wilcoxon

Need to consider overall richness ?

Dao *et al.*, 2015, Gut

Akk and metagenomics species!



GU:154 *A. muciniphila*

26 MGS associated with *A. muciniphila*

MGS not association with *A. muciniphila*

Carlota Dao *et al.*,

13 Firmicutes, 5 Bacteroidetes, 1 Actinobacteria and 1 Euryarchaeota

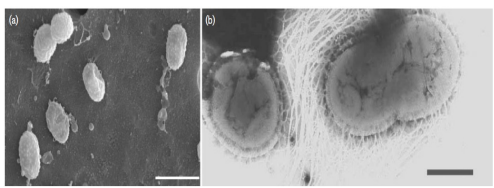
Weight loss programs: Reversion ?

Models:

Dietary Intervention
"MicroObese"

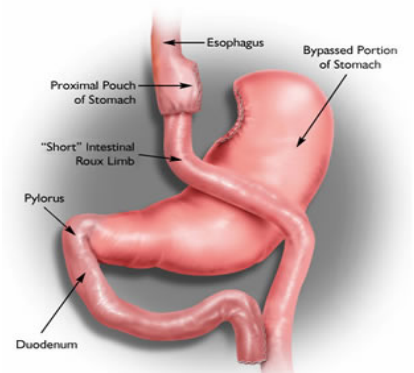
Cotillard A, Nature, 2013
Kong LC, AM J Clin Nut 2013
DAO, MC, GUT, 2015
Schoaie, Cell Metab, 2015

Future Probiotics ?



Akkermansia
& others

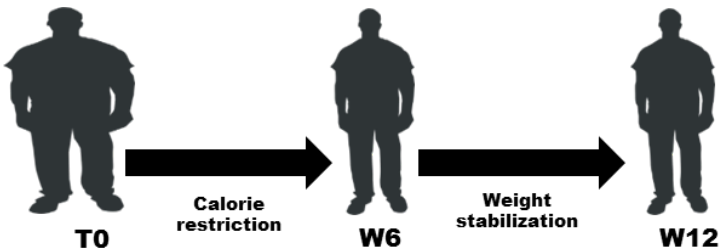
Bariatric Surgery
(PHRC microbaria)



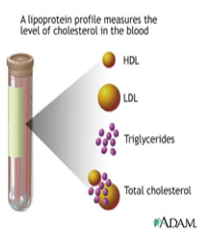
Furet at al, Diabetes, 2010
Kong, Am J Clin Nutr, 2013
Kong, Plos One, 2014
Aron-Wisnewsky J,
Curr Atheroscler Rep et al 2014
Review Nat Rev Gastroenterol
Hepatol, et al 2012
Magalhaes I, JCI, 2015
Monteiro-Sepulveda M, Cell Metab
2015

Dietary changes impact on richness

Obese or overweight patients (N=49)
Diet: High fiber and protein,
low carbohydrate index

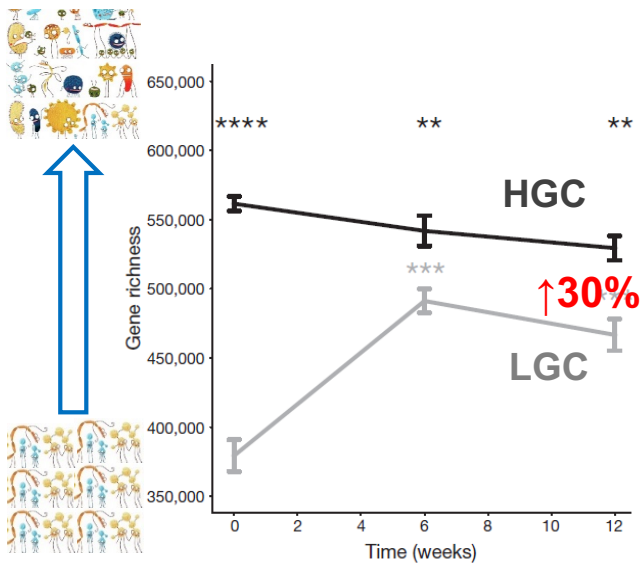


Diet



Phenotype

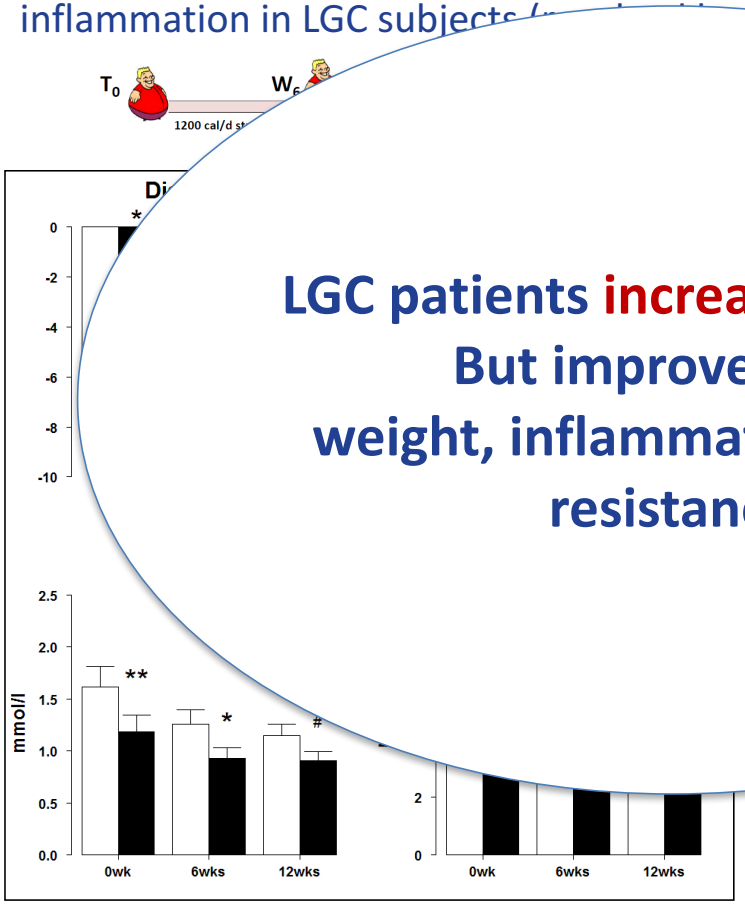
Gut flora*



Cotillard *et al.* Nature 2013

Gut microbiota diversity and response to dietary intervention

- More pronounced dys-metabolism and a tendency to higher low-grade inflammation in LGC subjects (r… their metabolic profile)



LGC patients increased diversity
But improved less
weight, inflammation, insulin resistance

…0.05, **: p-
…nitney tests.
…lculated by
…d and insulin values.

Cotillard *et al.* Nature 2013

MicroObese Dietary intervention

1200 kcal/d

35% proteins, 25% lipids, 40% CHO *vs* **25% proteins, 31% lipids, 44% CHO**




Topinambour/Artichoke*






Orge



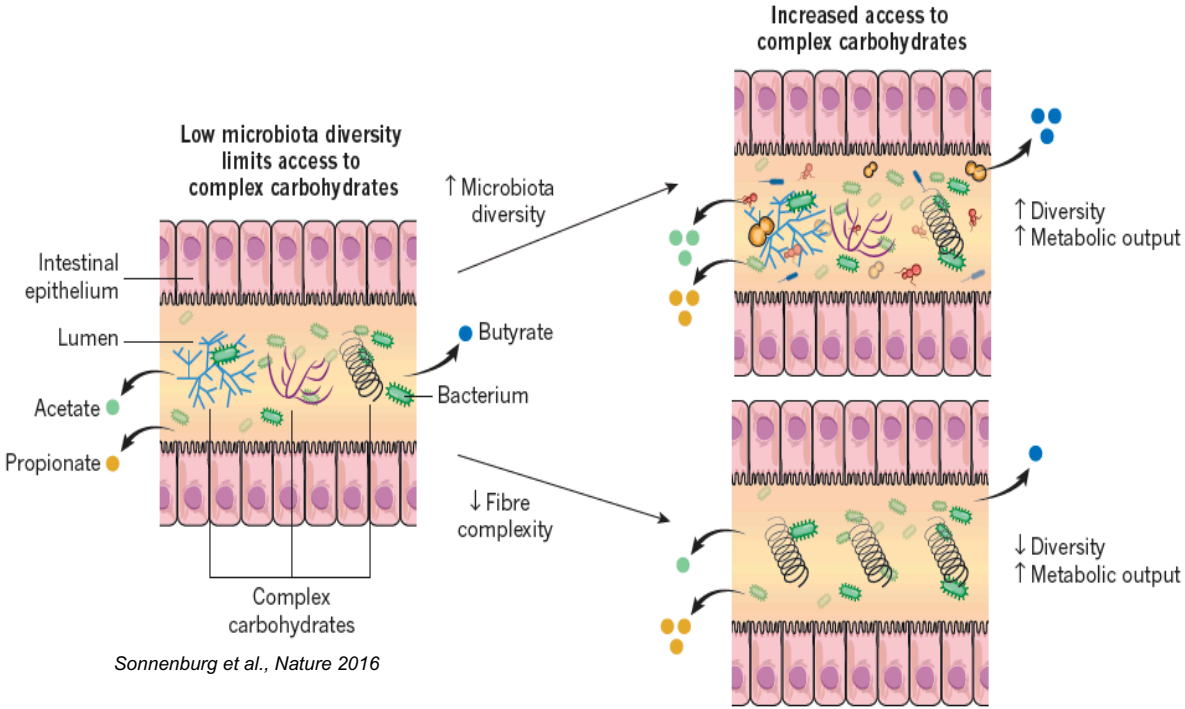







** Riche en Fructane (inuline, oligosaccharides)*

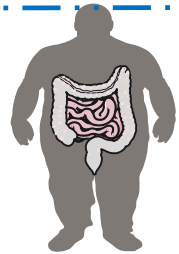
Baseline metagenomic diversity, diet and host metabolism



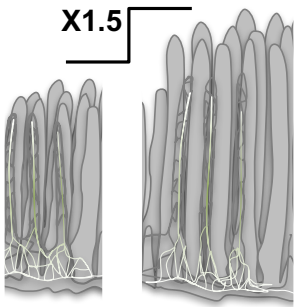
Sonnenburg et al., Nature 2016

Dietary interventions may have different effects depending on gut microbiota composition

Jejunum immunity is altered in obesity



Increased surface of absorption



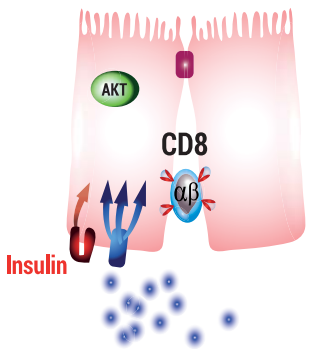
More inflammation (jejunum)

	n/mm2	Ob vs.Lean
Mature DC	5	x 5
NK cells	12	x 6
Macrophage	150	x 1.5

CD8αβ

Ob vs. Lean		n/mm2
Lamina propria	350	x 1.75
Epithelium	1200	x 1.5

Altered function (insulin resistance)



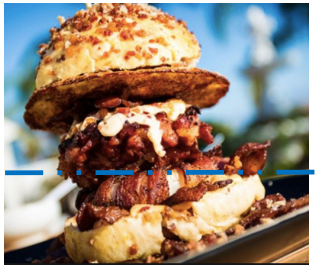
GM-CSF, IFN-γ, TNF-α, IL-10, IL-17, IL-22

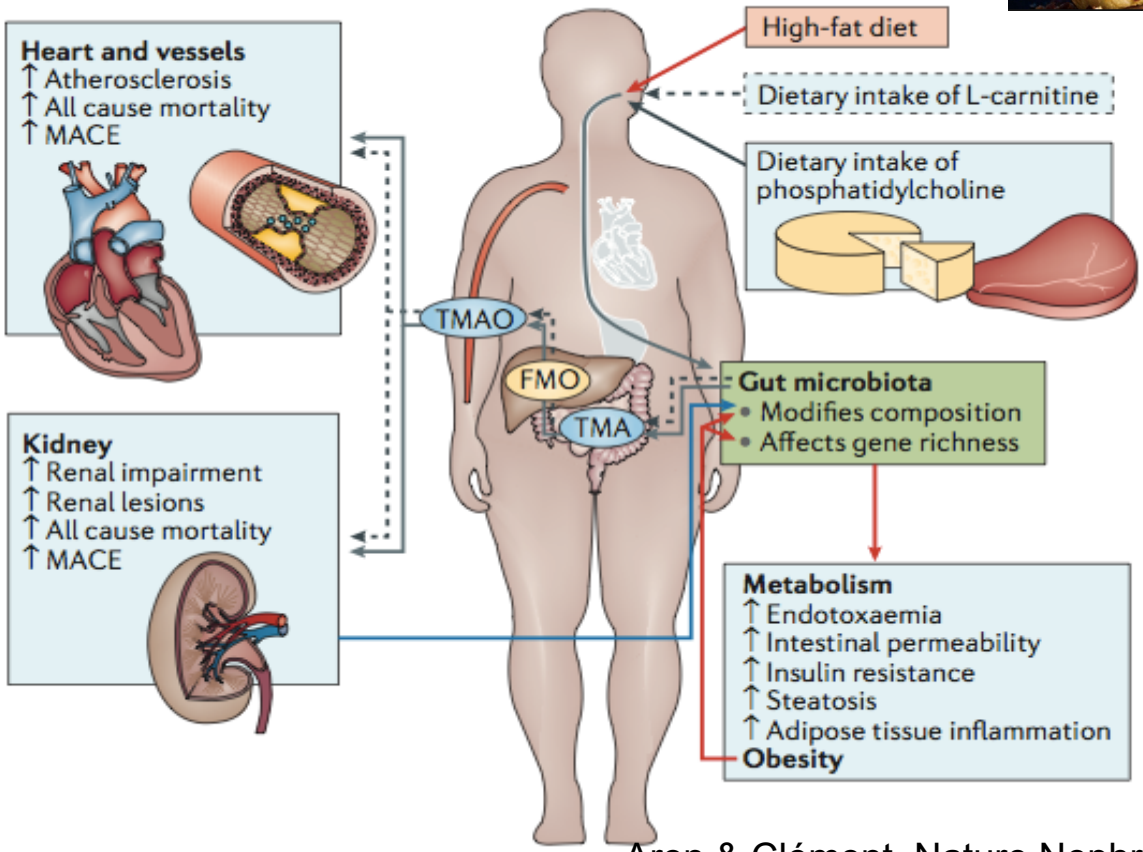
Links with obesity & complications

Corpulence, liver disease and dyslipidemia

Monteiro-Sepulveda *et al.* Cell Metab 2015

Gut-derived metabolites : ex TMAO?



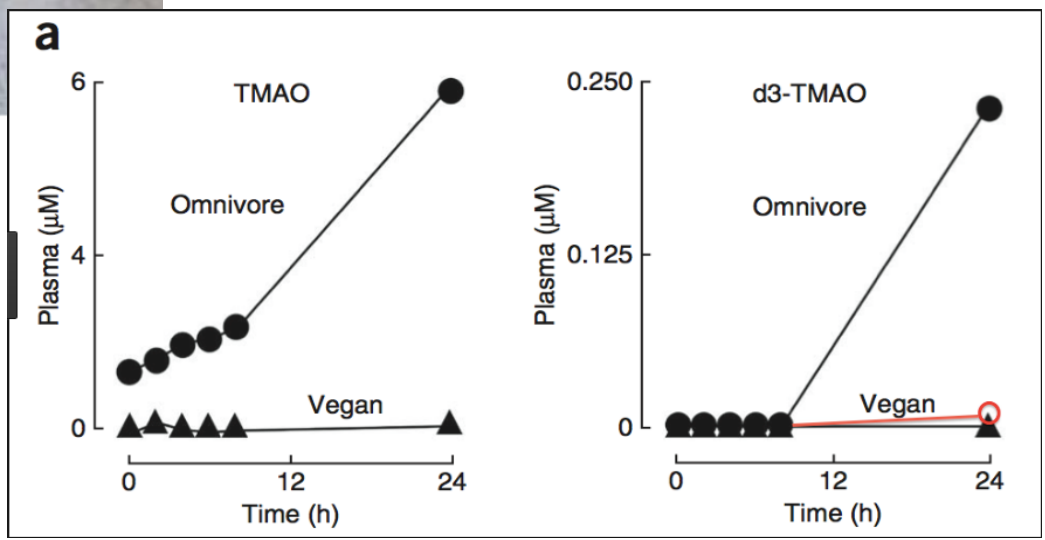


Aron & Clément, Nature Nephr, 2016

Specific microbiome in humans

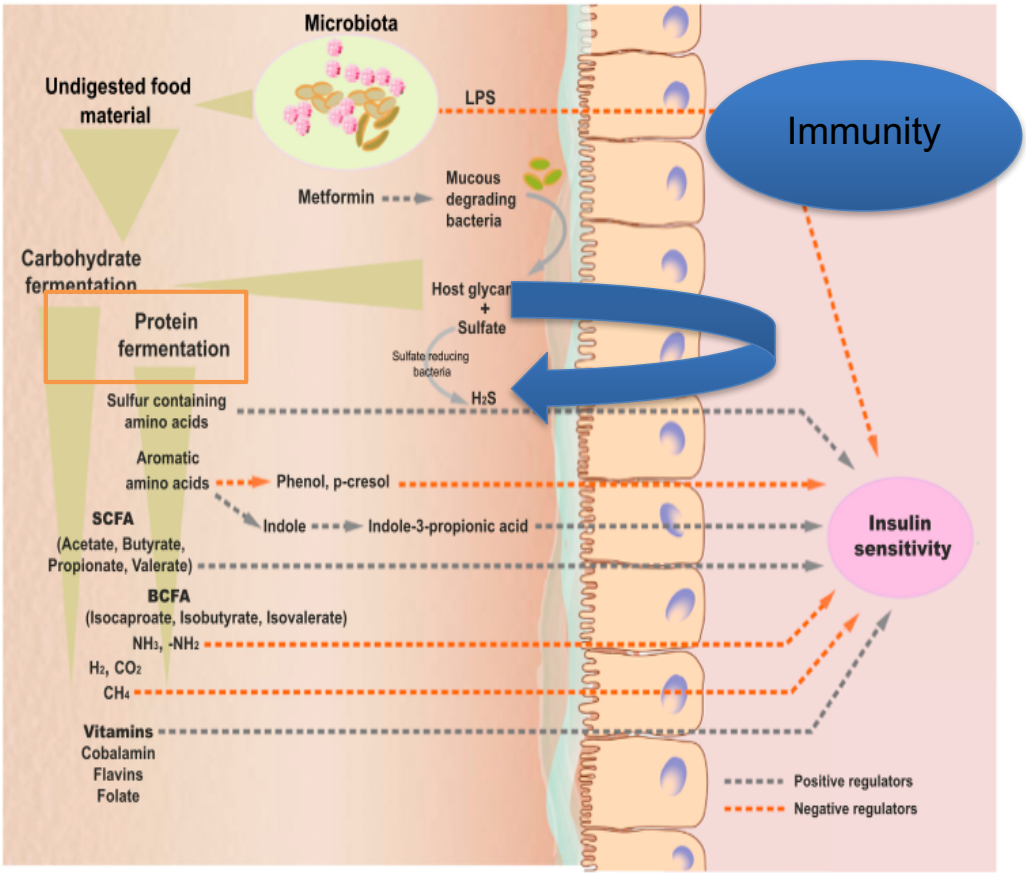
Ex Vegan

Low interindividual variations



Eur J Nutr. 2016

More than TMAO



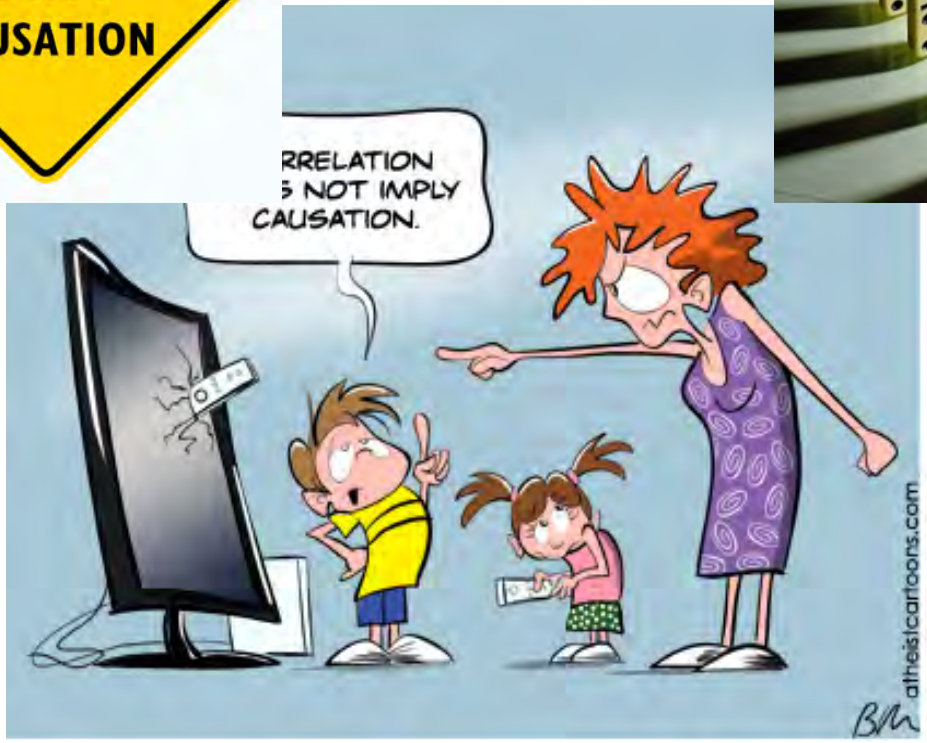
Intestinal barrier

Diet matters

Host metabolism & Inflammation matter

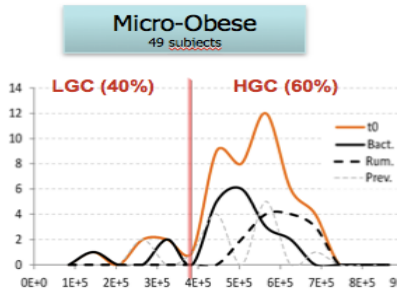
Adapted from Khan MT, et al, Cell Metab 2014


CORRELATION
IS NOT
CAUSATION

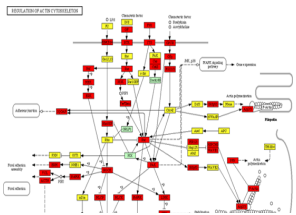

RRELATION
5 NOT IMPLY
CAUSATION.
atheistcartoons.com

To the future ?

Toward the future

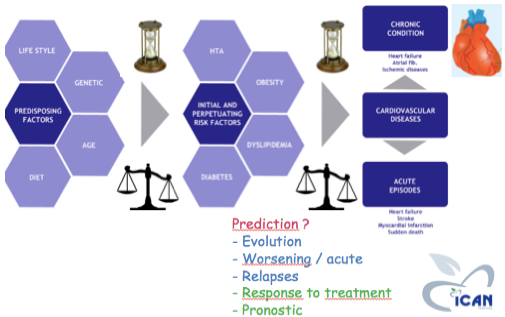


Cotillard, Nature 2013

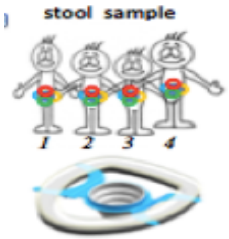


- Low diversity & Richness
- Different bacterial groups (MGS)
- **Functional changes (Ecosystem)** ?

New Diagnostics/predictors Of response ?



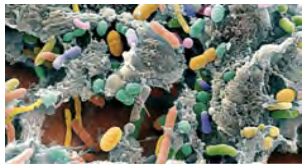
Response to Drugs Individual profiles ?



Optimal Treatments ?

- Nutrition-based
- pre, probiotics or combination
- Bacterial modulation
- Gut microbiota (auto-transfer)

Can the micro[illegible] treatment **for human[illegible]ease ?**



Efficiency ?
For which objective ?

Food ?
Prebiotics?
Probiotics?
Metabolites ?
Feces transfer ?
Combination?

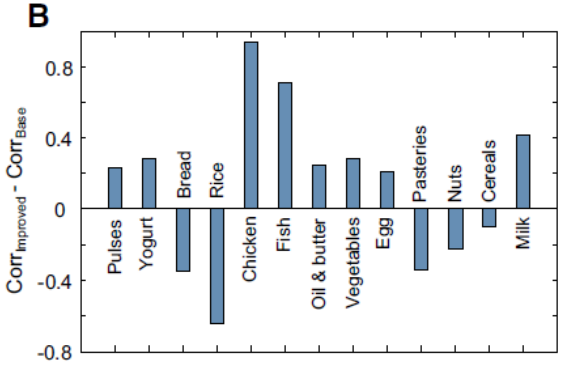
Microbiome ?
Gut barrier ?
Derived-molecules?
Host targets?
Combined?

Patients Phenotypes
Heterogeneity
Healthy stages of obesity?

Prevention ?
Patient trajectories?
Stage of progression?

Vers une Nutrition de précision

Microbial richness
Microbial function
Species (*A. muciniphila*)
Metabolites (SCFA, TMAO)
Environmental factors (diet)



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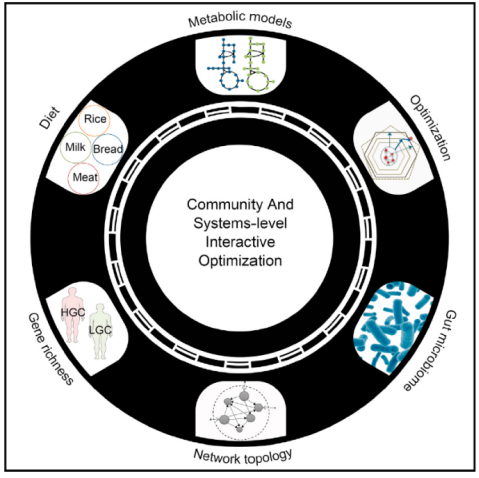

lbox

Shoaie *et al.* Cell Metab 2015 & Dao *et al.* CNX 2016

nutriomics

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