Microbiote, Obésité et atteintes Rénales

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Journée Mondiale du Rein

Obesity & Cardiometabolic disorders

- 192 Billion Euros / year EU (57% direct cost 21% loss of productivity , 22% indirect cost) *Leal J. et al, 2012, Economic Costs In: European Cardiovascular Disease Statistics).*
- Worldwide progression obesity & diabetes & CVD incl. Children
- Expected Tsunami
- Socio economic disparities
- Attrition in CVD & Metabolic drugs
- Need for new approaches !

6.5 MILLION
OBESE PEOPLE IN FRANCE

500 MILLION
OBESE PEOPLE WORLDWIDE

3 MILLION
PEOPLE WITH DIABETES IN FRANCE

17.3 MILLION
ANNUAL DEATHS WORLDWIDE
DUE TO CARDIOVASCULAR DISEASE

LEADING
CAUSE OF DEATH
WORLDWIDE

Obesity and kidney disease: Hidden consequences of the epidemic

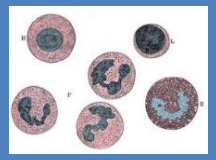
Csaba P. Kovesdy, Susan L. Furth, Carmine Zoccali,
on behalf of the World Kidney Day Steering Committee

First published: 16 February 2017 Full publication history

Journal of Renal Care

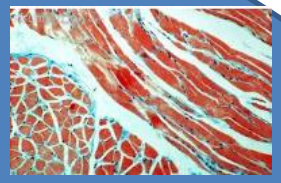
……Obésités : Maladie d'organes, Maladie des systèmes….

Modes de vie

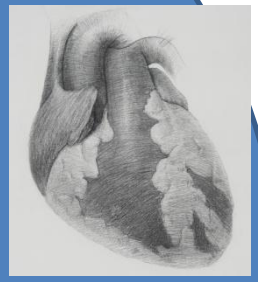


Système immun
Production cytokine

Cerveau
Système endocrine
humeur



Muscle
Fonction
Endocrine

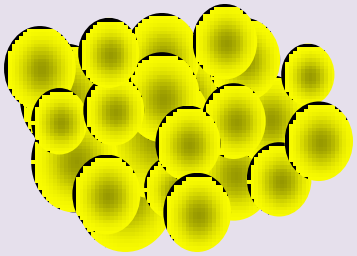


Coeur

Fonctions
Endocrines
perturbées

Hypertrophie

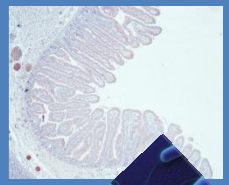
altérations
Immuno
inflammatoires

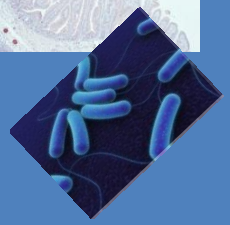


Fibrose

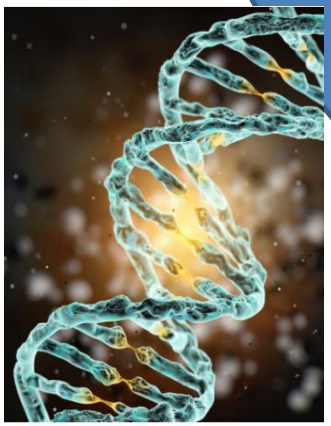
Angiogenese

Dysfonction
Organelle

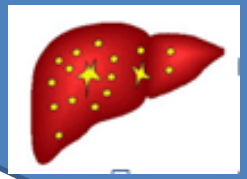




Intestin
Microbiote



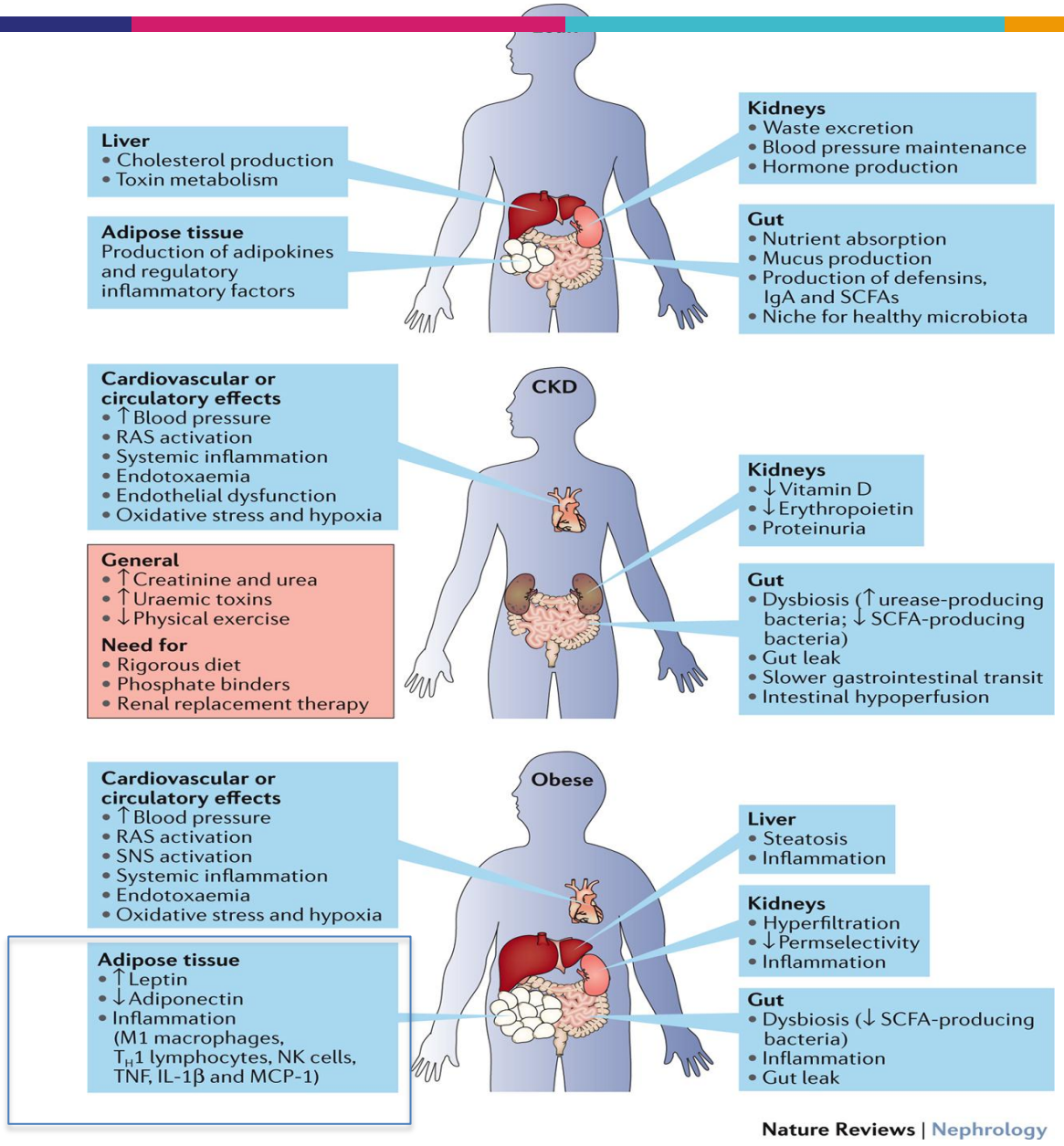
Génome/Epigénome



Foie
NAFLD/NASH

Système
Vasculaire
Atherothrombo

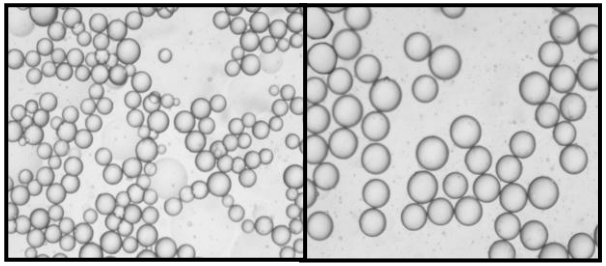
The fat–intestine–kidney axis



Câmara, N. O. S. *et al.* (2017) Kidney disease and obesity: epidemiology, mechanisms and treatment *Nat. Rev. Nephrol.* doi:10.1038/nrneph.2016.191

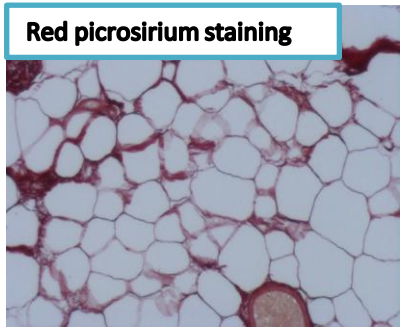
Pathological alterations of Human adipose tissue obesity

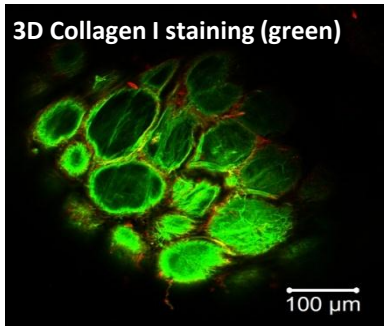
Adipocyte hypertrophia



Lean Obese

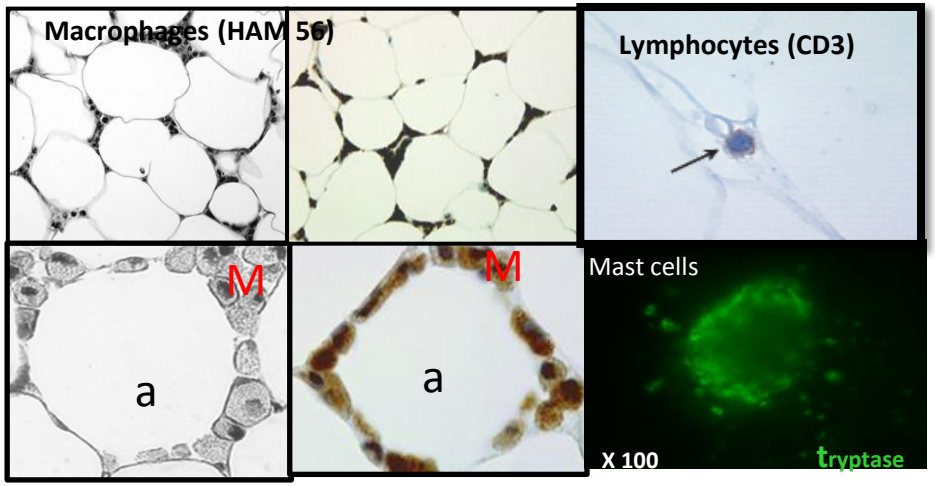
Fibrosis (pericellular)





Divoux, Diabetes 2010 *Pellegrinelli, U872*

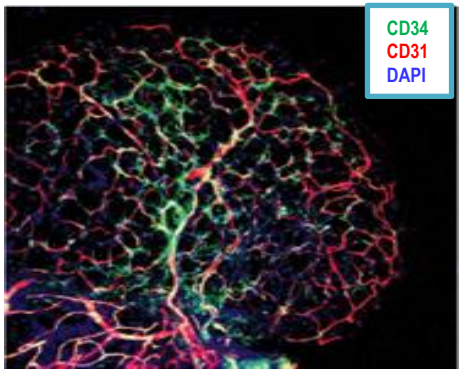
Inflammatory cell accumulation

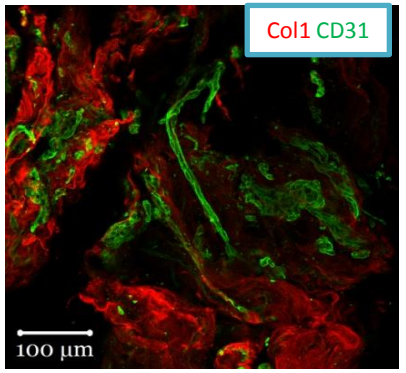


Macrophage (M) accumulation **Other immune cells**

Cancello, Tordjman, Diabetes 2010 U872

Vascular alterations (inflammation & senescence)





Villaret, Diabetes 2010, U *Pellegrinelli, U872*

Liu, Divoux Nature Medicine, 2009

Adipose- Inflammatory Cell Crosstalks

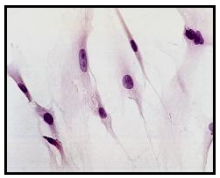
Local interactions

Macrophages
M1/M2 state
Polarization
***Ex. KLF4* (Coll)**
J Clin Invest 2011

TNFa, IL-6
CCL5/Rantes
CXCL2

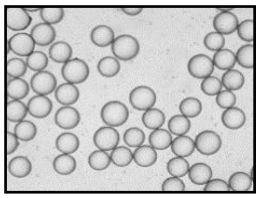
Keophiphath, ATVB. 2010
Rouault, Endocrinology, 2013

NEFA?



Proliferation,
Migration,
Inflammation
Profibrotic
Profibrotic progenitors

Lacasa, Endocrinology 2007
Keophiphath ,Mol Endoc 2009
Marcellin Cell Metab 2017



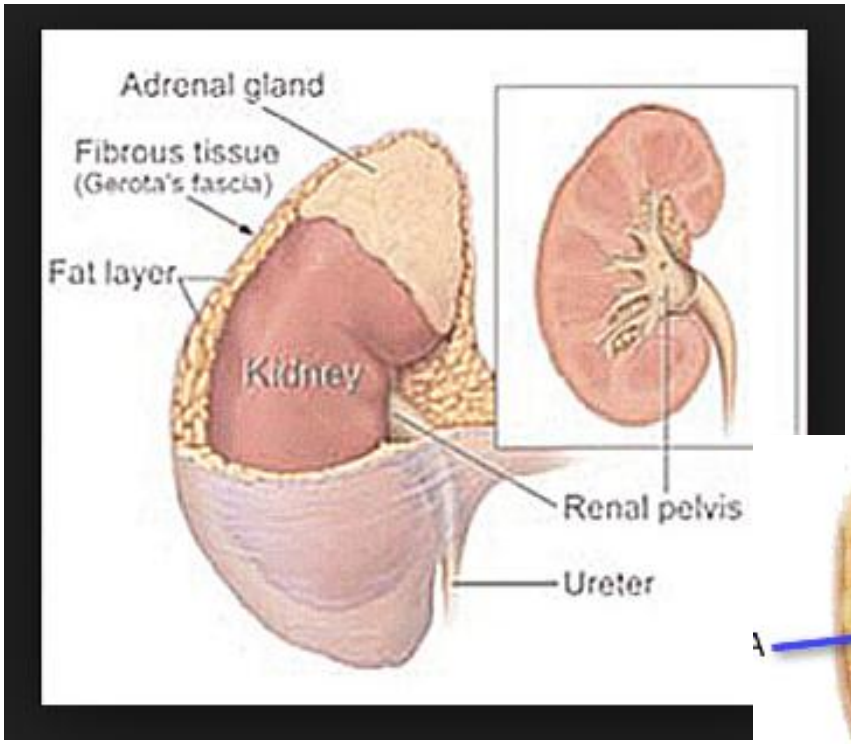
Organelle Dysfunctions
Lysosomes etc..
Soussi (Diabetes, 2016)

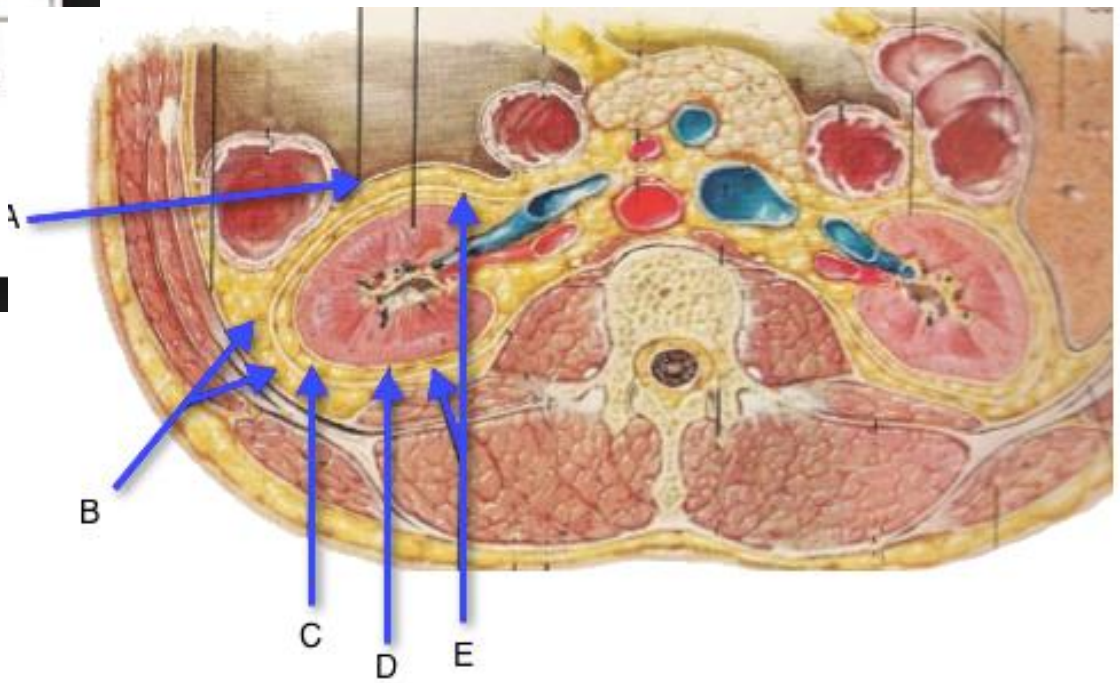
Inflammation
GPS2 (A Toubal, JCI, 2013)

Metabolic perturbations
Glucose uptake
Insulin sensitivity

Pelllegrinelli, J Pathol 2014

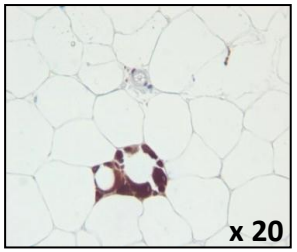
Fat Layer around Kidney





Adipose tissue Macrophages & liver & heart diseases

Obesity



Insulino-resistance

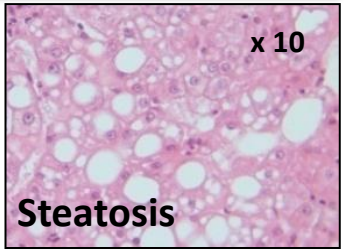
Accumulation of macrophages in omental AT & deap scWAT

Future Avenues
Cytokines (IL-6) ?
Fatty acids ?

Chronic & intermittent Hypoxia

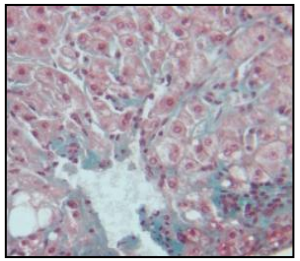
Steatosis

Fibro-inflammation



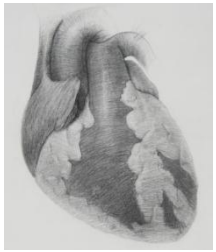
Cancello Diabetes 2006
Tordjman J Hepatol 2009
TAM Diabetes 2011
Tordjman J Hepatol 2012
Bedossa Hepatology 2012
Aron J Hepatol 2012
Venteclef Eur. Heart J 2015
Bedossa Gut, 2016

Inflammation

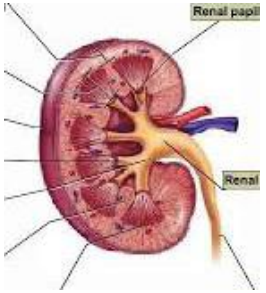


Fibrosis

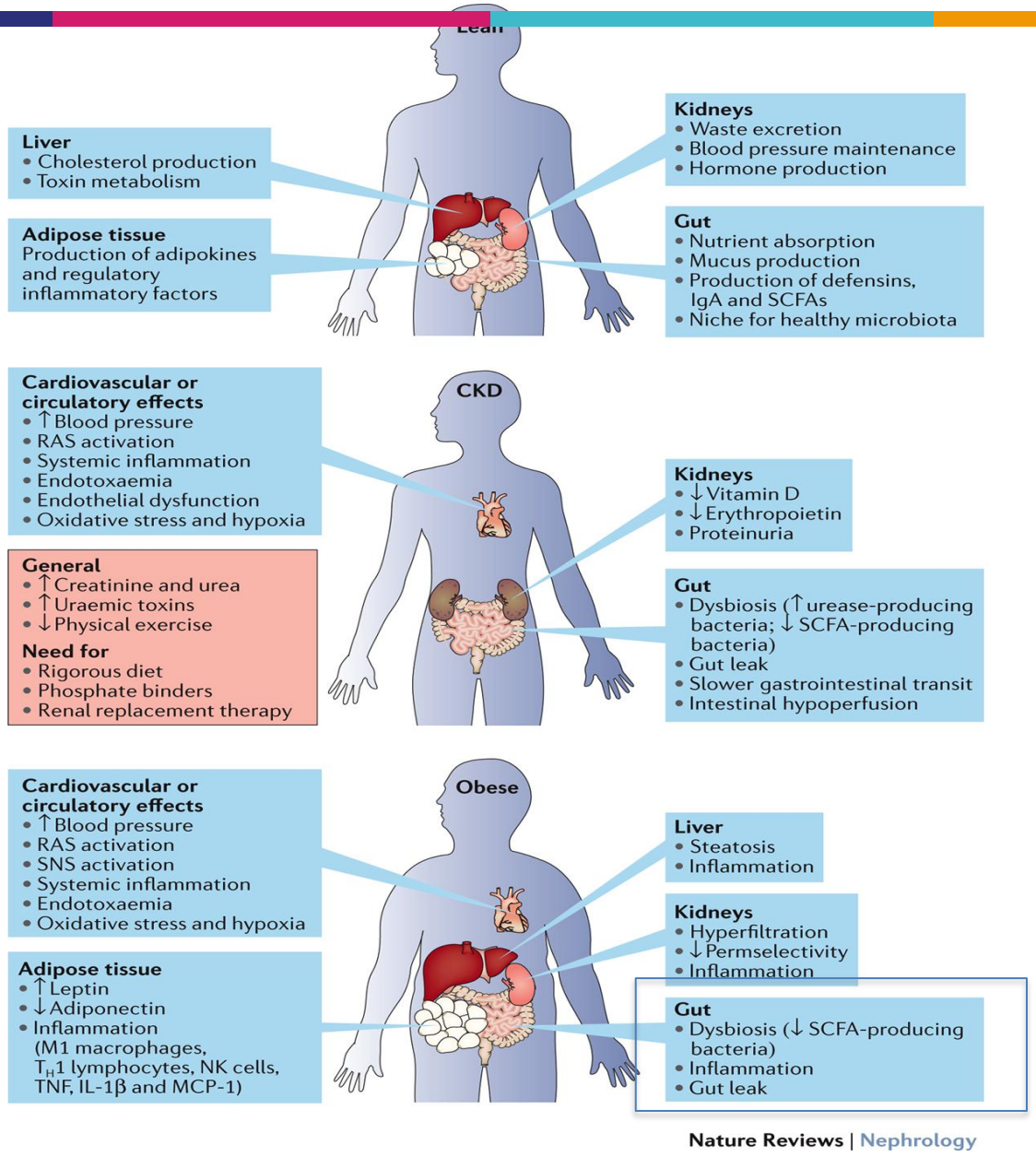
x 10



?

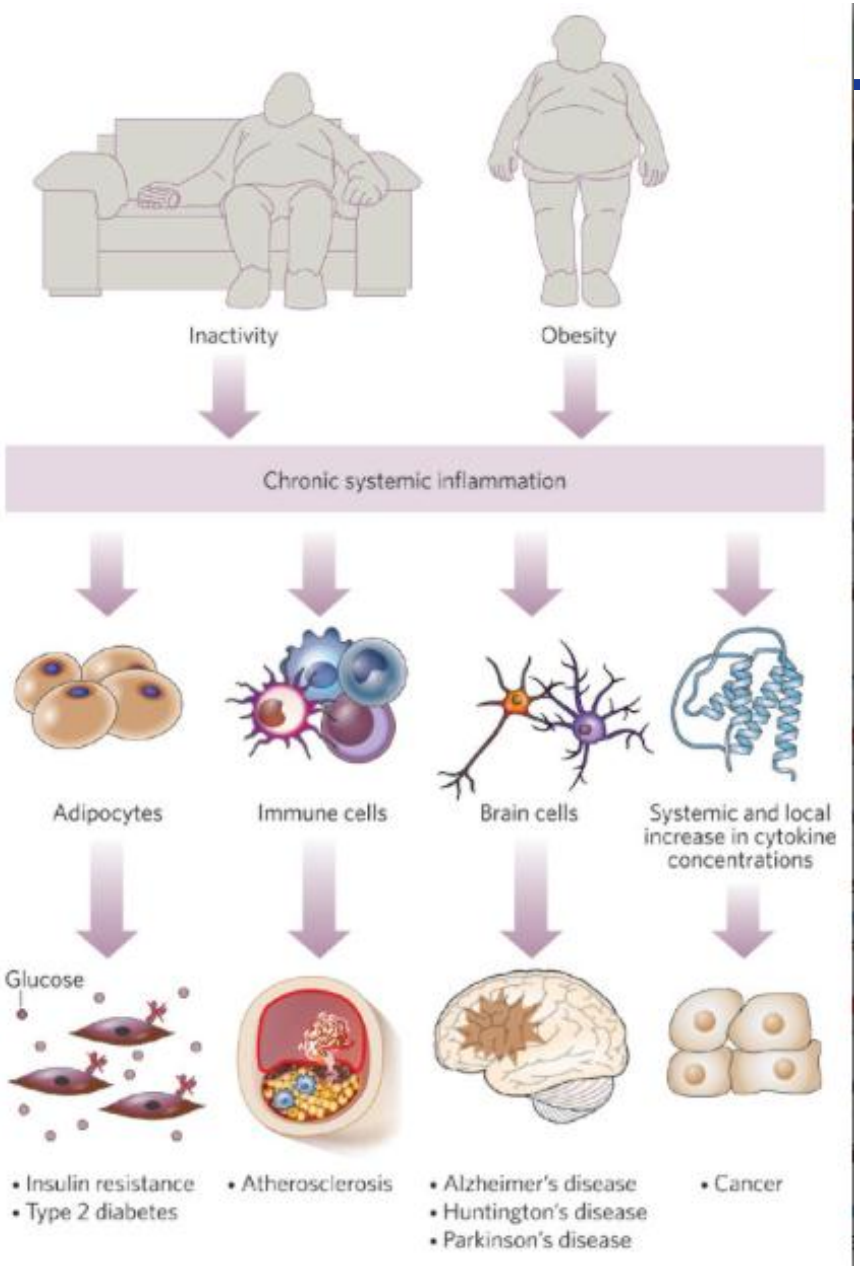


The fat–intestine–kidney axis

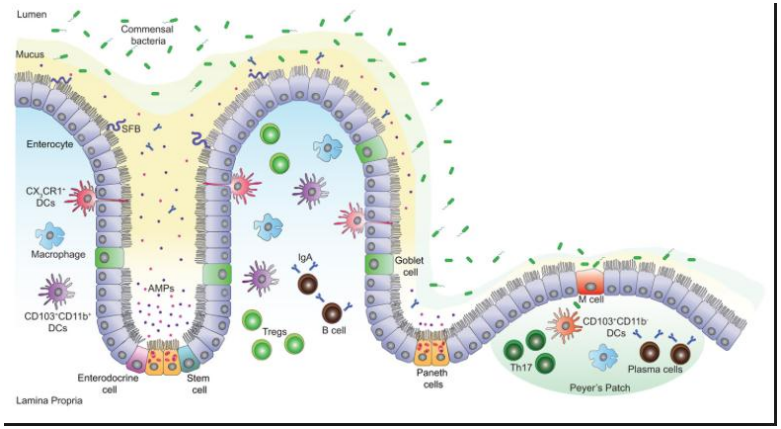


Câmara, N. O. S. *et al.* (2017) Kidney disease and obesity: epidemiology, mechanisms and treatment
Nat. Rev. Nephrol. doi:10.1038/nrneph.2016.191

"Nutritional changes" & low grade inflammation : GUT?

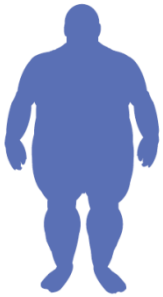


What about intestinal barrier?



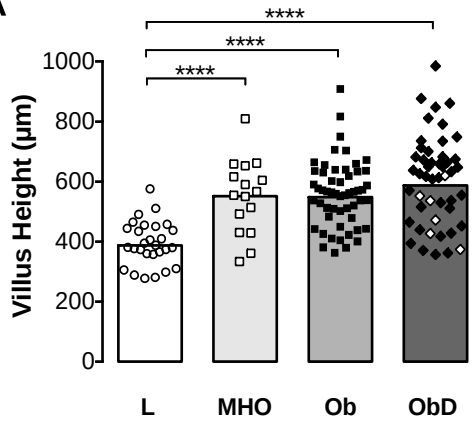
- Largest lymphoid tissue in size of the body: complex immune system
- Dysbiosis of gut microbiota in obesity *(Cotillard et al., Nature 2014)*.
- **Gaps in knowledge in obesity-related inflammation of the jejunum**

Summary of findings



Increased surface of absorption

A



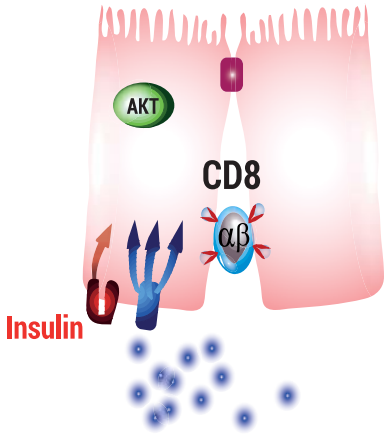
More inflammation (jejunum)

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

CD8αβ

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

Altered function (insulin resistance)



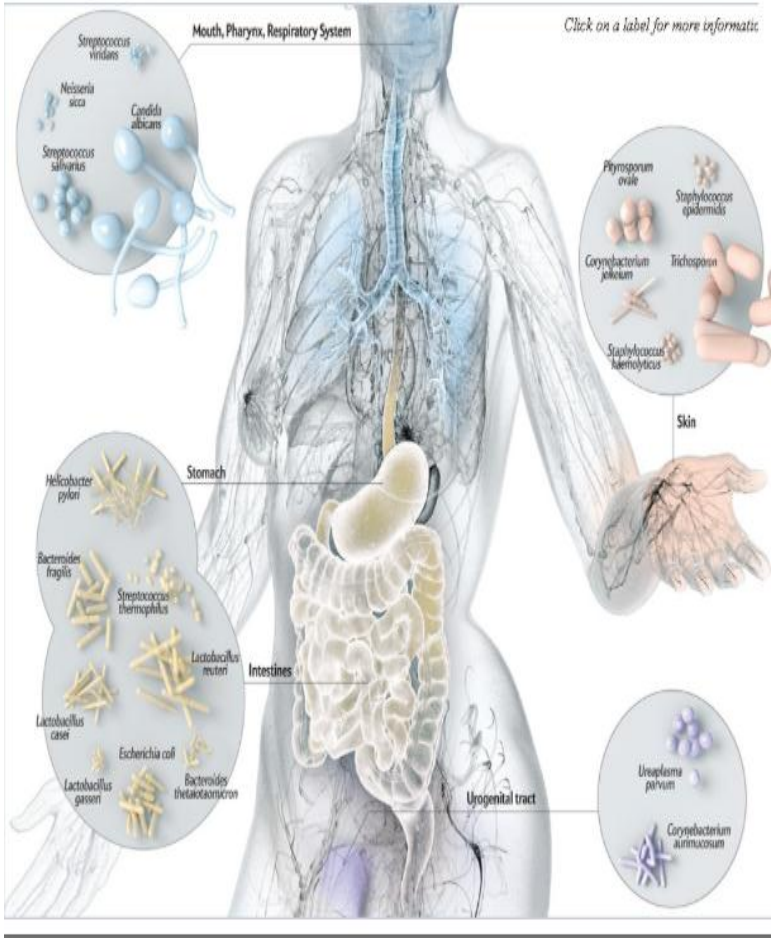
GM-CSF, IFN-γ, TNF-α, IL-10, IL-17, IL-22

Links with obesity & complications

Corpulence, liver disease and dyslipidemia

Monteiro-Sepulveda *et al.* Cell Metab 2015

Microbiota & Diseases: a Quick Overview



Microbiota as an asset

- Defense - bacterial antagonism
- Priming of mucosal immunity
- Peristalsis
- Metabolism of dietary carcinogens
- Synthesis of B & K vitamins
- Epithelial nutrients (e.g. SCFAs)
- Degradation of Dietary Oxalate++
- Conversion of prodrugs
- Utilisation of indigestible **$(CH_2O)n$**

Microbiota as a liability

- Procarcinogens → carcinogens
- Overgrowth syndromes
- Opportunism – Translocation
- Implicated in obesity, metabolic syndrome and colorectal cancer, IBD and other diseases (CKD…)

Thanks to J. Marchesi

Gut Microbiome & Obesity: Diet matters

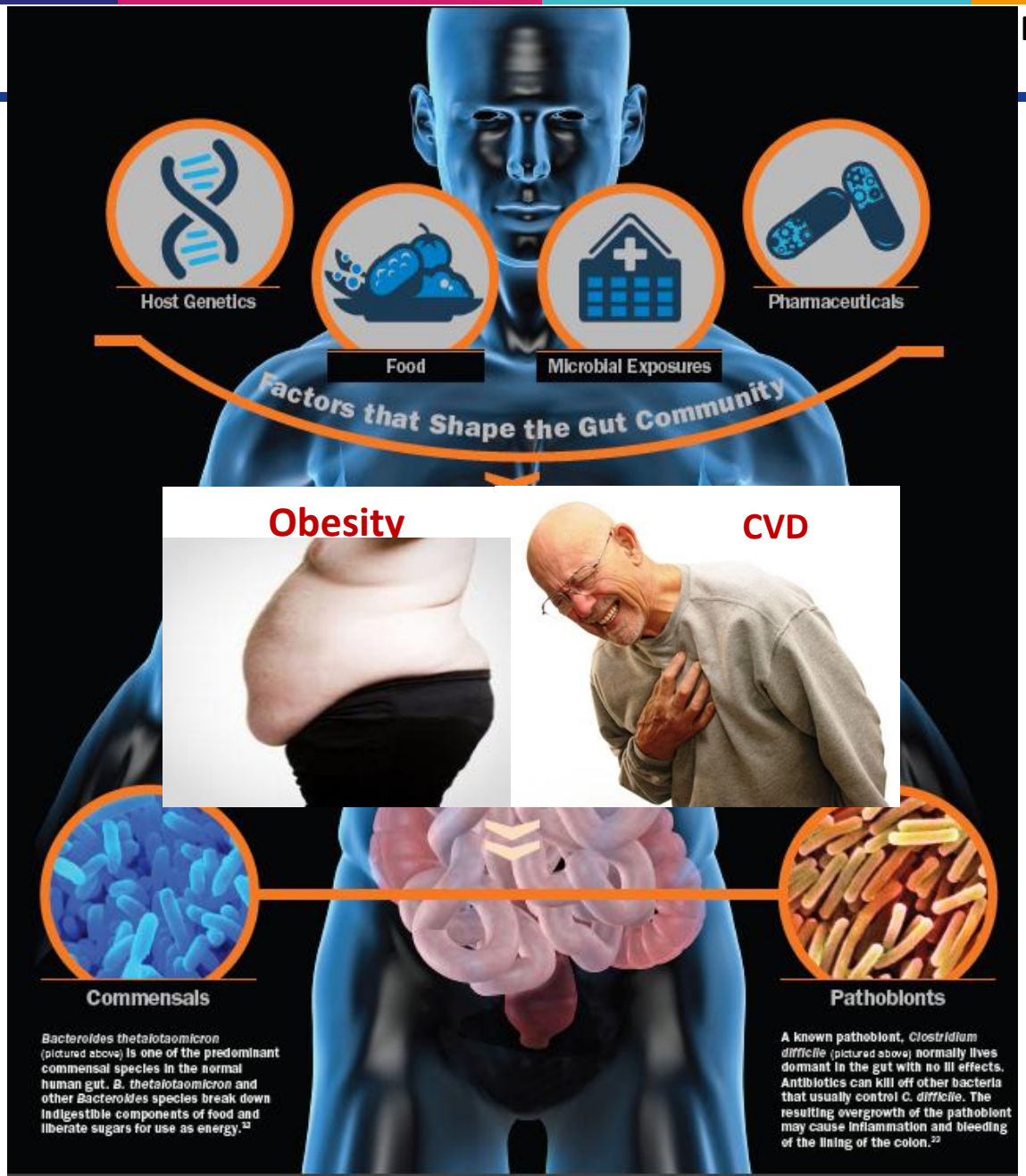
Protective role of gut microbiota from lean donnor in presence of « healthy diet »

Protection lost with « unhealthy diet »

Ridaura *et al.*
Science 2013

➢ **Gut Microbiome could be one of the causes of Obesity**

Equilibre entre santé et maladie



Fibromyalgia

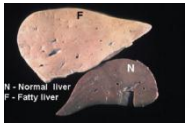
IBD

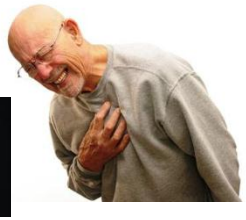
Diabetes

T I & T II

Colon Cancer

NASH





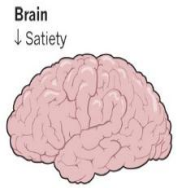
CVD

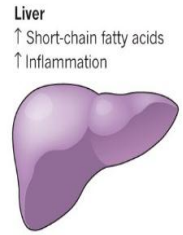
Depression

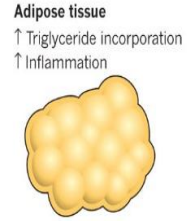
Kidney stones

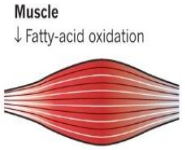
Atopic disease

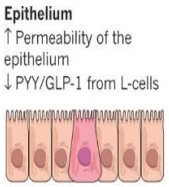
Potential role for microbiota in the development of cardiometabolic (&Kidney) diseases

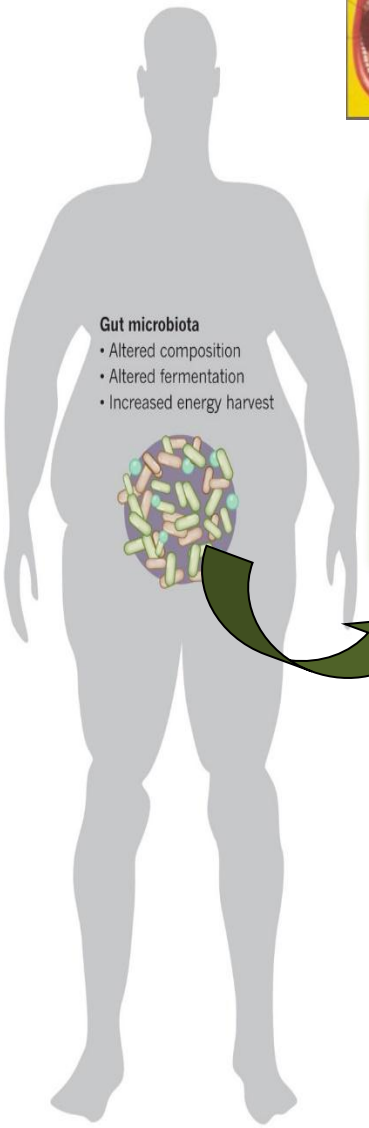


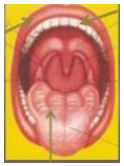












Buccal microbiota (Koren O et al. PNAS. 2011 or Hyvärinen K et al. 2012, Atherosclerosis, 2012

Gut microbiota Composition:

Gene richness

Specific species or bacterial groups

Bacterial Metabolites *(i.e. SCFA, TMA, TMA0) Other Pcresol, indoxyl sulfate*

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

↓

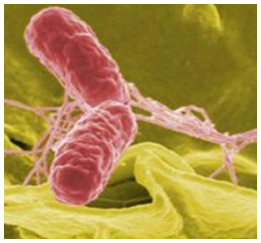
Insulin resistance

↓

Metabolic syndrome

↓

Chronic disease (CVD, T2D)

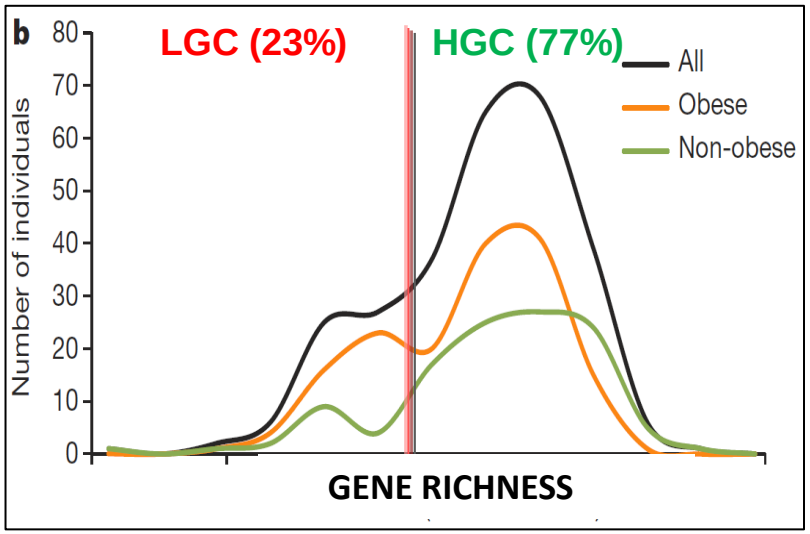


Tremaroli *et al.* Nature 2012

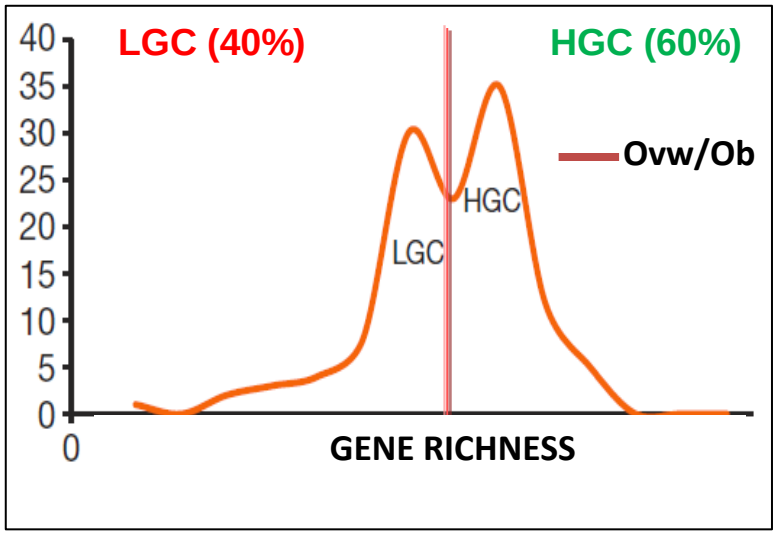
Adapted from Harris *et al.* J Obes 2012

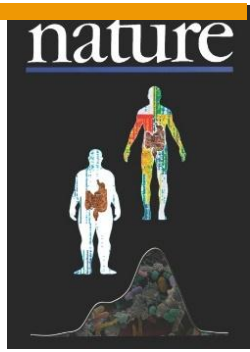
Gut Microbiome and Obesity: Diversity matters

METAHIT
292 subjects



MicroObes
49 subjects





LGC = Low gene count

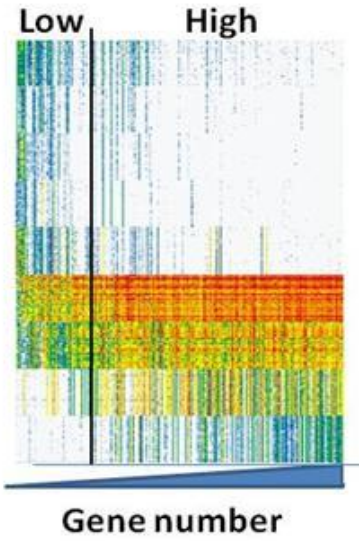
HGC = High gene count

LGC: ↗ Pro-inflammatory

- *Cl. bolteae*
- *Cl. symbiosum*
- *Cl. clostridioforme*
- *Cl. ramosum*
- *R. gnavus*

LGC: ↘ Anti-inflammatory

- *F. prausnitzii*
- *R. inulinivorans*
- *Co. eutactus*
- *M. smithii*

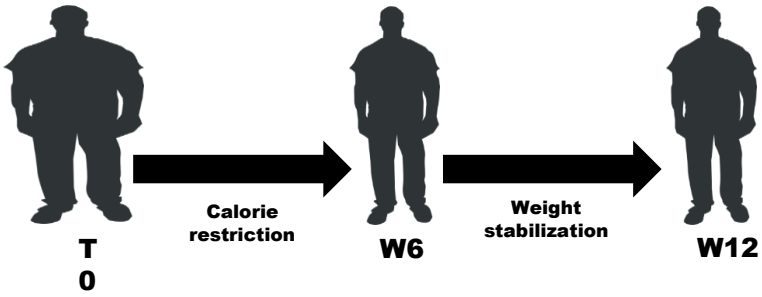


LGC associates with CMD risks

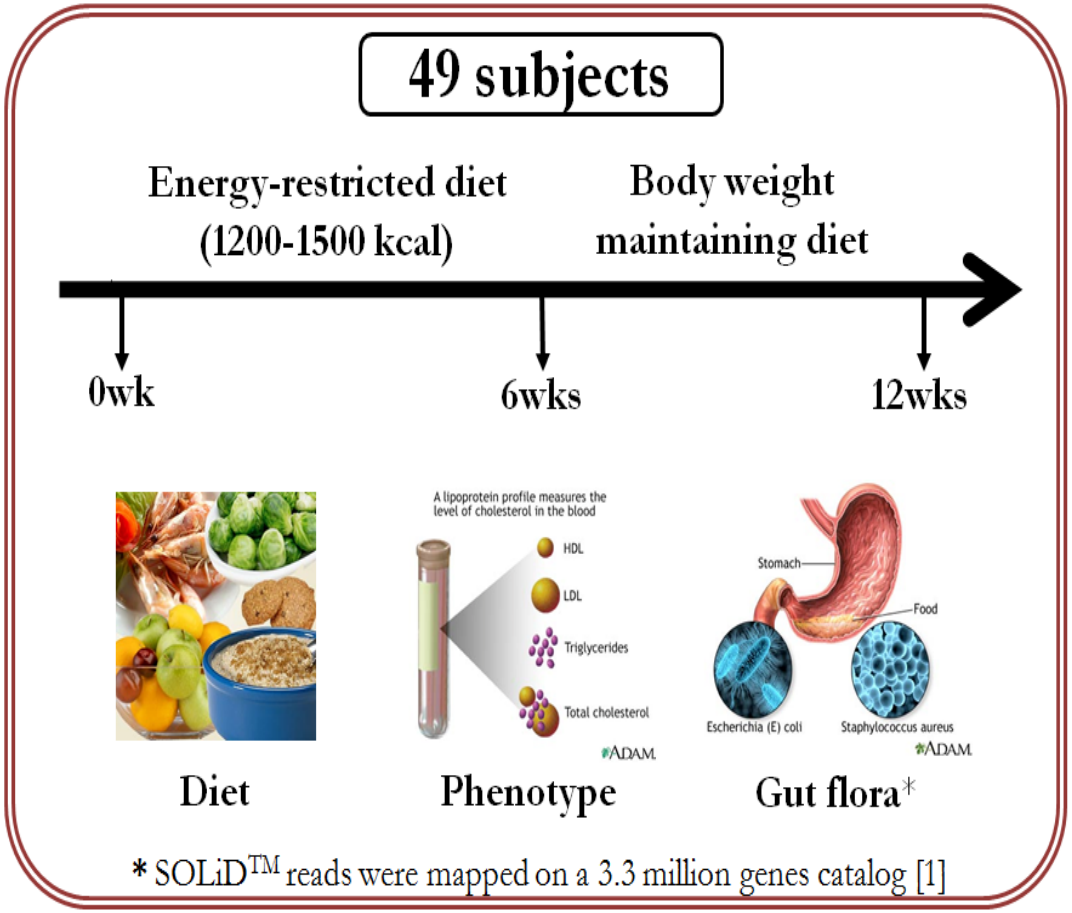
- ↑↑ dyslipidemia
- ↑ adiposity
- ↑ insulin resistance (surrogates)
- ↑ inflammation (circulating and adipose tissue)

Le Chatelier *et al.* Nature 2013;
Cotillard *et al.* Nature 2013

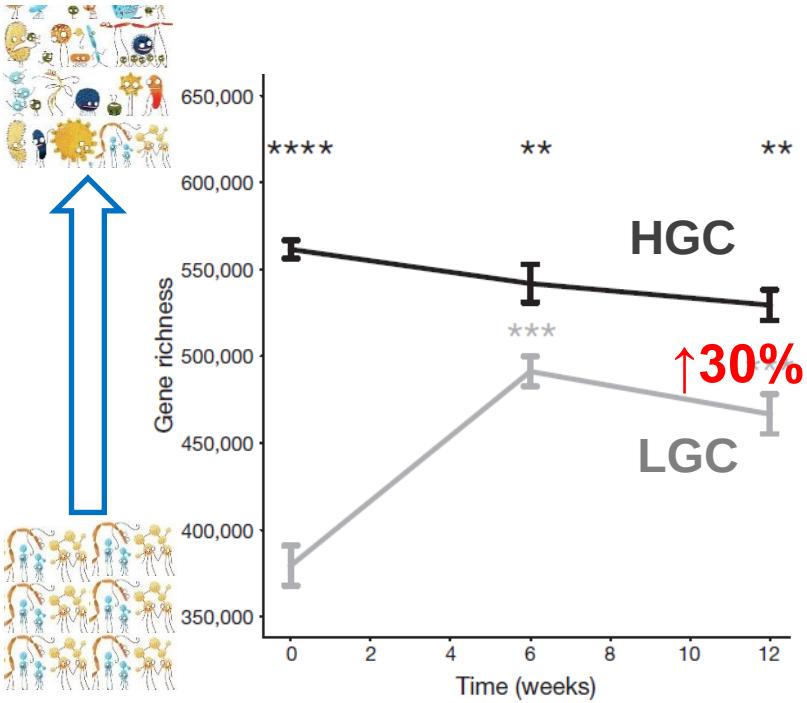
Dietary intervention, phenotypes and Gene richness: MicroObes study



49 obese or overweight patients
Diet: High fiber and protein, low carbohydrate index



[1] Qin J. et al., g. Nature, 464 7285:59-65, 2010.

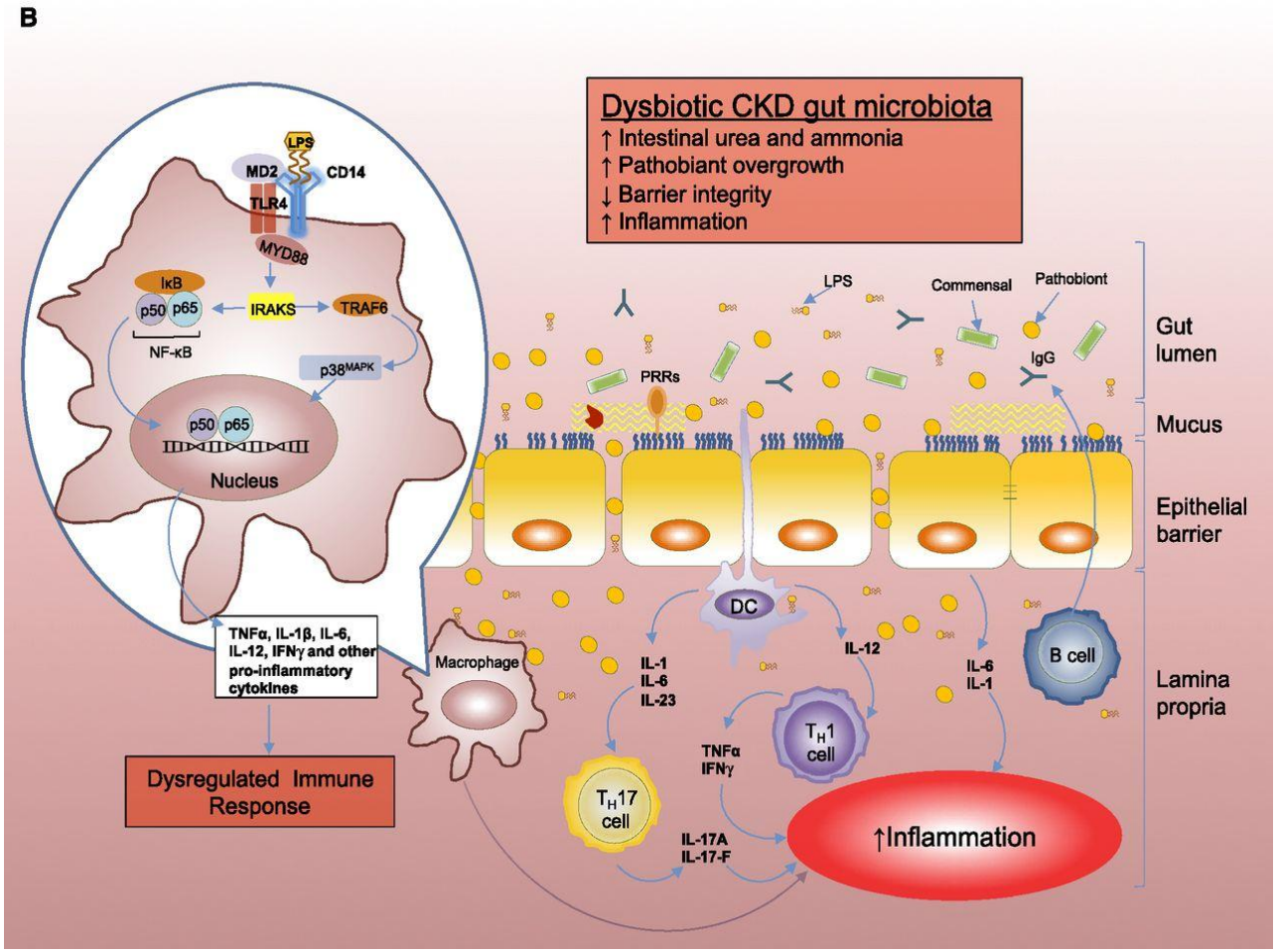


Cotillard *et al.* Nature 2013

Qualitative and quantitative alterations in CKD ?

- *ESRD patients*: 190 OTU phyla Firmicutes (subphylum Clostridia), Actinobacteria & Proteobacteria (Gammaproteobacteria) Vaziri ND, Kidney Int (2013)
- Nephrectomized rats: 175 OTU. Dec Bacteroidetes & Firmicutes, *especially Lactobacillaceae and Prevotellaceae*
- ESRD vs. healthy : enrichment in bacteria producing urease and uricase and less SCFA (Wong J, Am J Nephrol. 2014)
- CKD : more Firmicutes > bacteroidetes (Barros AF, 2015)
- ESRD patients (Pyrosequencing) > *Klebsiella*, *Proteus*, *Escherichia*, and *Pseudomonas* (Wang et al,)
- Lower richness species; lactobacillus & prevotellacae (Vaz
- **Bacterial translocation** ? / LPS (Wang et al, 2012)

Bidirectional dialogue



Bacteria release uremic toxins (cleared by the Kiney)

……

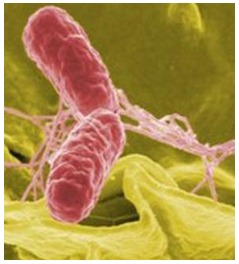
Others
Dietary fibers
Antibiotics
Slow transit
Acidocetosis
Oral iron

……

Ali Ramezani, and Dominic S. Raj JASN 2014;25:657-670

JASN

Microbiota, obesity and cardiovascular disease



Gut microbiota
Composition
Microbial richness
Specific species (i.e. A. muciniphila)

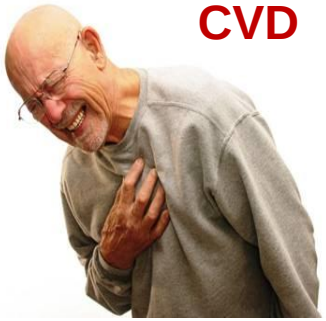
Metabolites
TMAO

Bacterial components
Cell wall, LPS

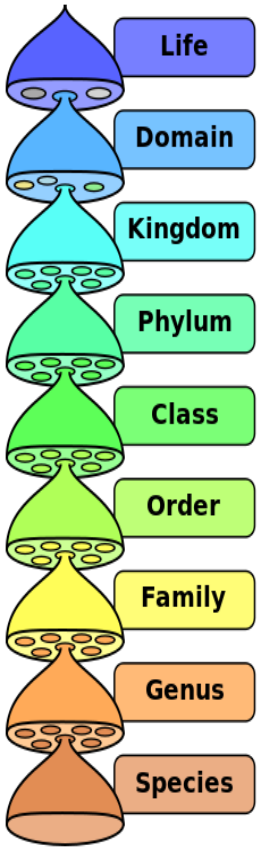
Obesity and co-morbidities

Obesity

CVD



Akkermansia muciniphila (Akk)



Bacteria

Verrucomicrobia

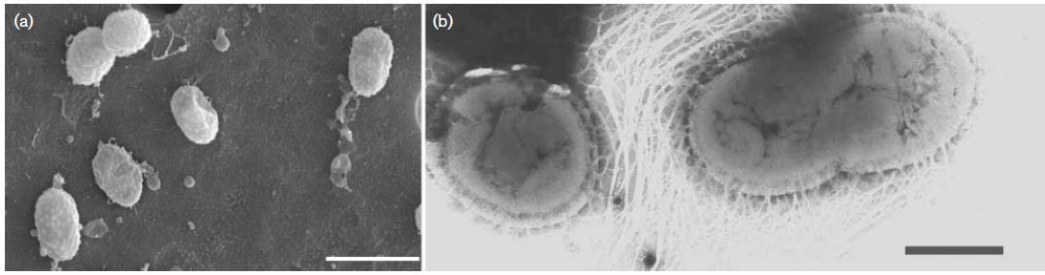
Verrucomicrobiae

Verrucomicrobiales

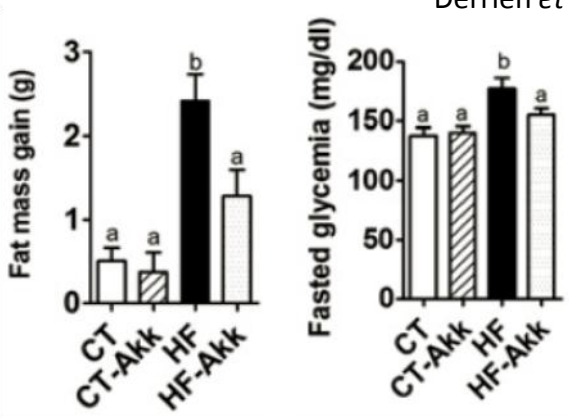
Verrucomicrobiaceae

Akkermansia

Akkermansia muciniphila

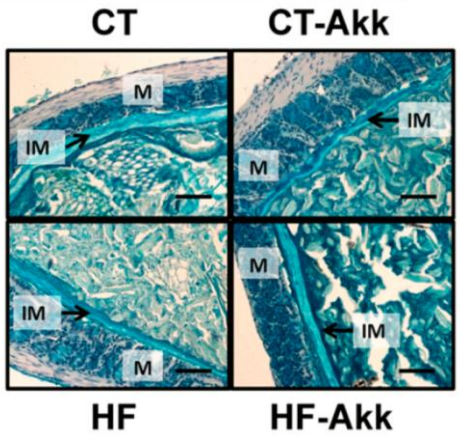


Derrien *et al.* IJSEM 2004



Health implications

- **Mouse studies: maintenance of glucose homeostasis.** *Everard et al. PNAS 2013*
- **Links with Metformin.** *Shin et al. Gut 2013*
- **Inverse association between Akk and iR humans (more clear in mice).**

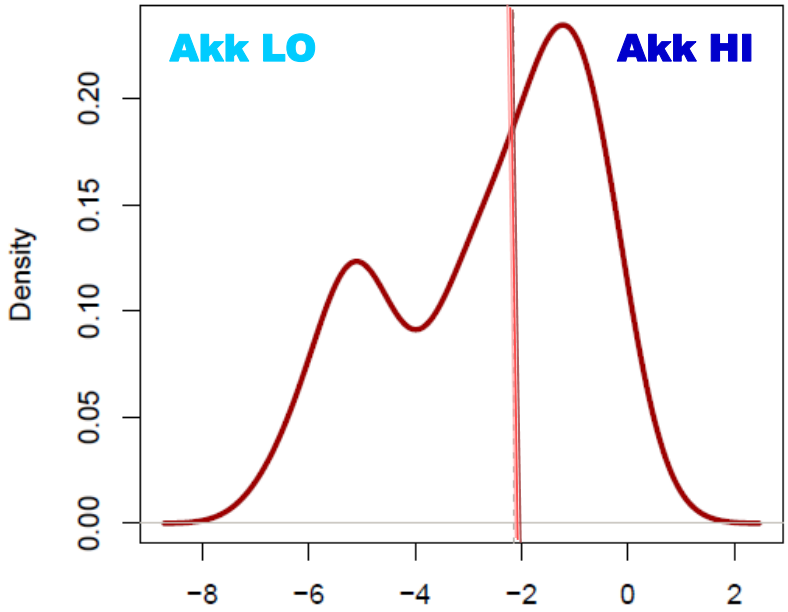


Everard *et al.* PNAS, 2013

AIM: Study the association between *A. muciniphila* abundance, metabolic status, and microbial richness

T0
49 overweight
and obese adults

Akk abundance distribution



Dao *et al.* Gut 2015

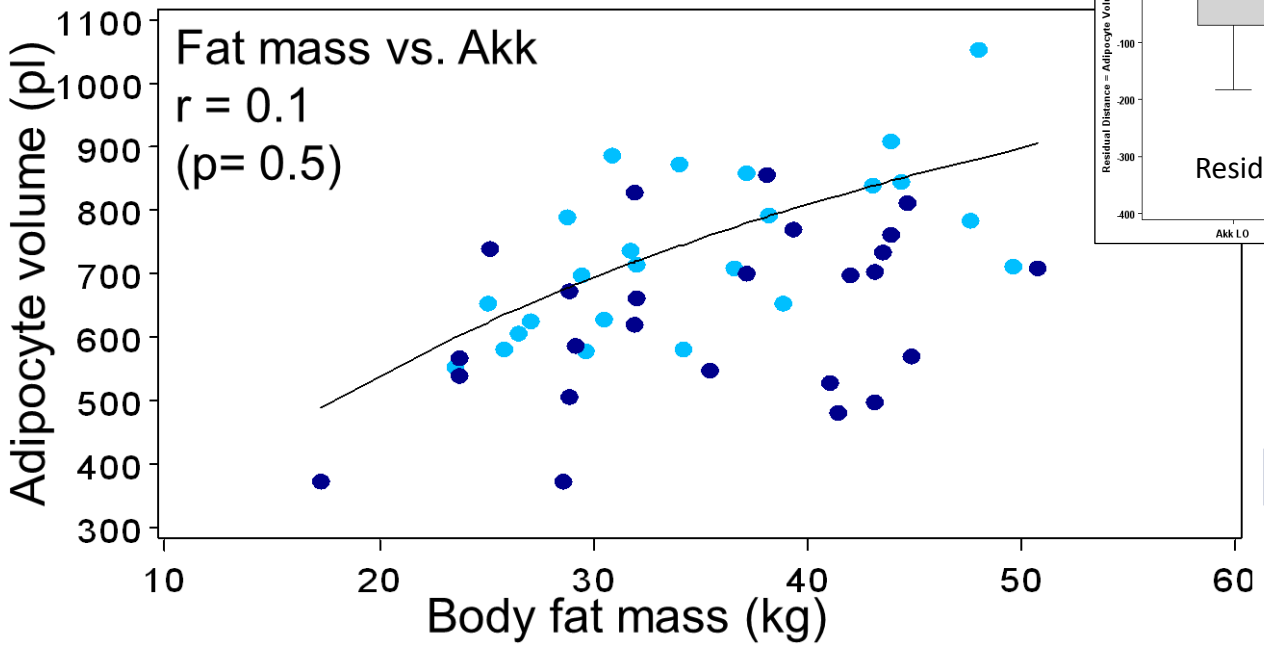
Higher baseline A. muciniphila is associated with a healthier metabolic status

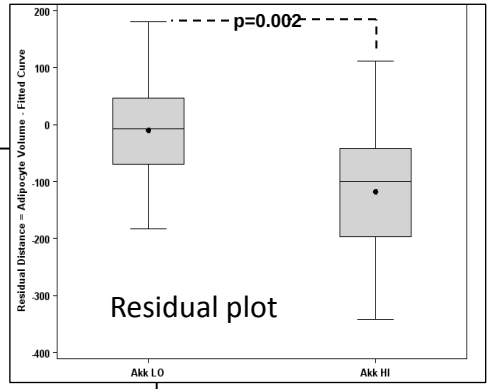
*p≤0.05, **p≤0.01

Cytoscape

Dao *et al.* Gut 2015

Subjects with higher A. muciniphila have smaller adipocytes





Akk LO

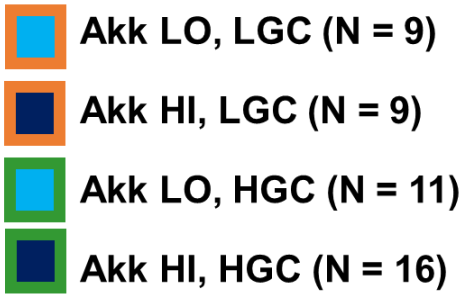
Akk HI

$$Theoretical\ Adipocyte\ volume\ (pl) = \frac{(40.7 * \text{Kg Fat Mass})}{(1 + (0.025 * \text{Kg Fat Mass})}$$

Methodology:
Hirsch et al. Lipid Res, 1968
Spalding et al. Nature, 2008

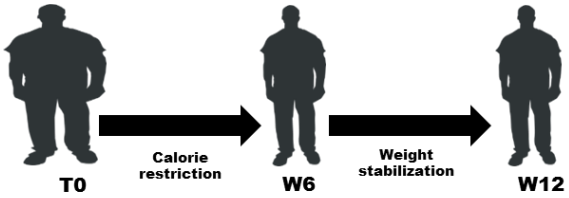
Dao *et al.* Gut 2015

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

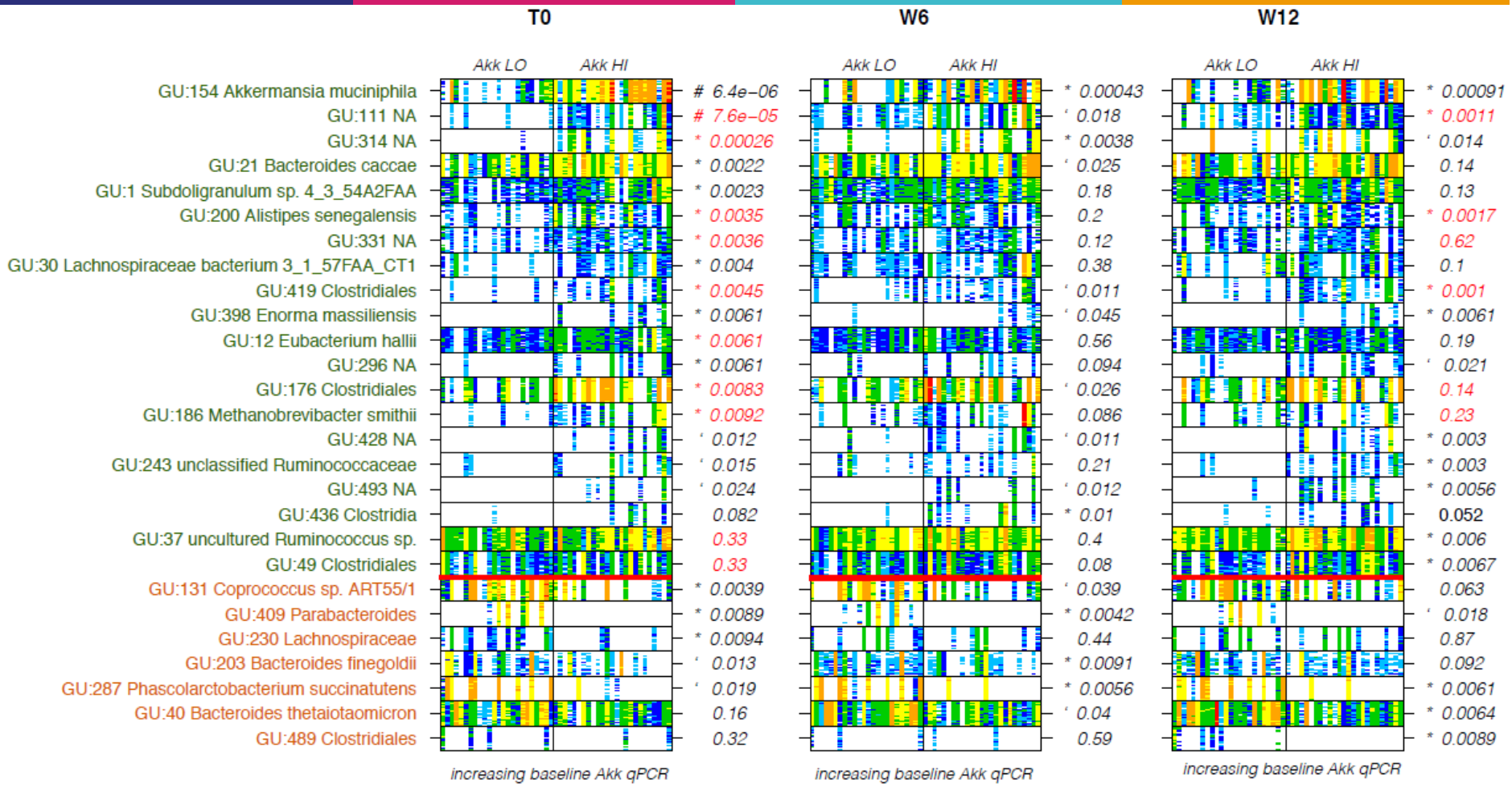


*p<0.05, **p<0.01; Kruskal-Wallis, Wilcoxon rank sum test, Bonferroni adjustment

Dao *et al.* Gut 2015



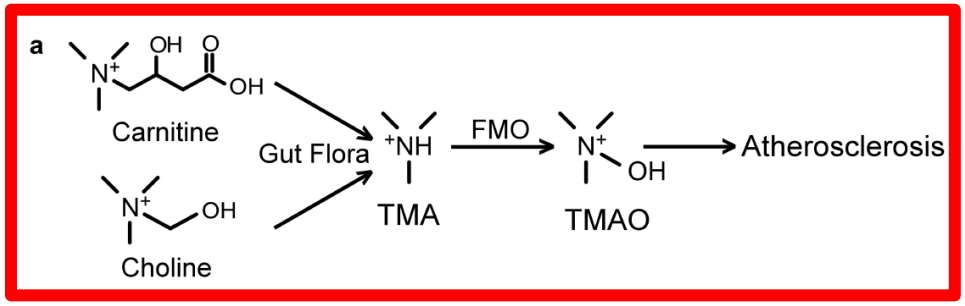
A core of MGS associated with Akk over time in MicroObes

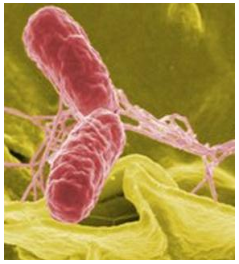


13 Firmicutes, 5 Bacteroidetes, 1 Actinobacteria and 1 Euryarchaeota

Dao *et al.* Gut 2015

Microbiota, obesity and cardiometabolic diseases





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Microbial richness
Specific species (i.e. A. muciniphila)

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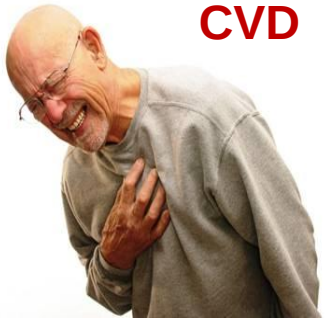
Bacterial components
Cell wall, LPS

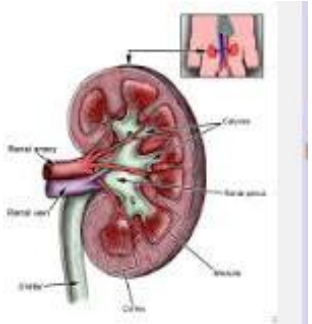
Co-morbidities

Obesity

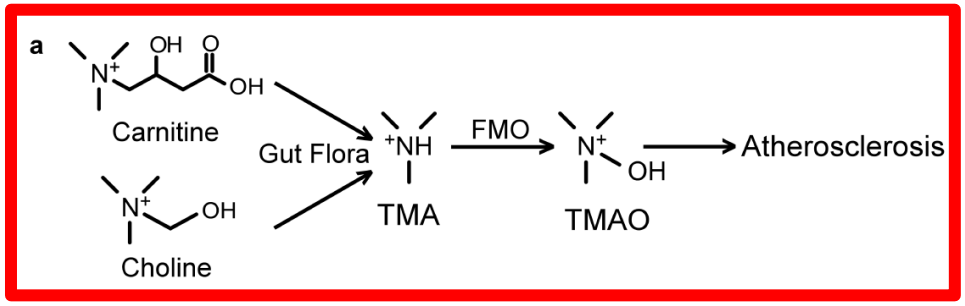
CVD

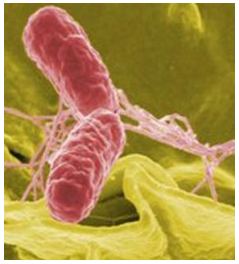


CKD?



Microbiota, obesity and cardiometabolic diseases





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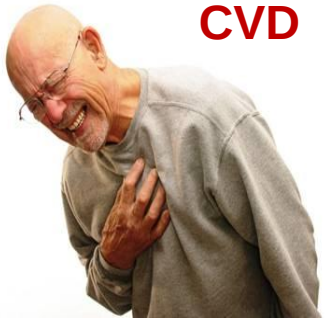
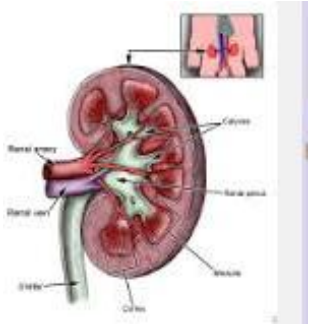
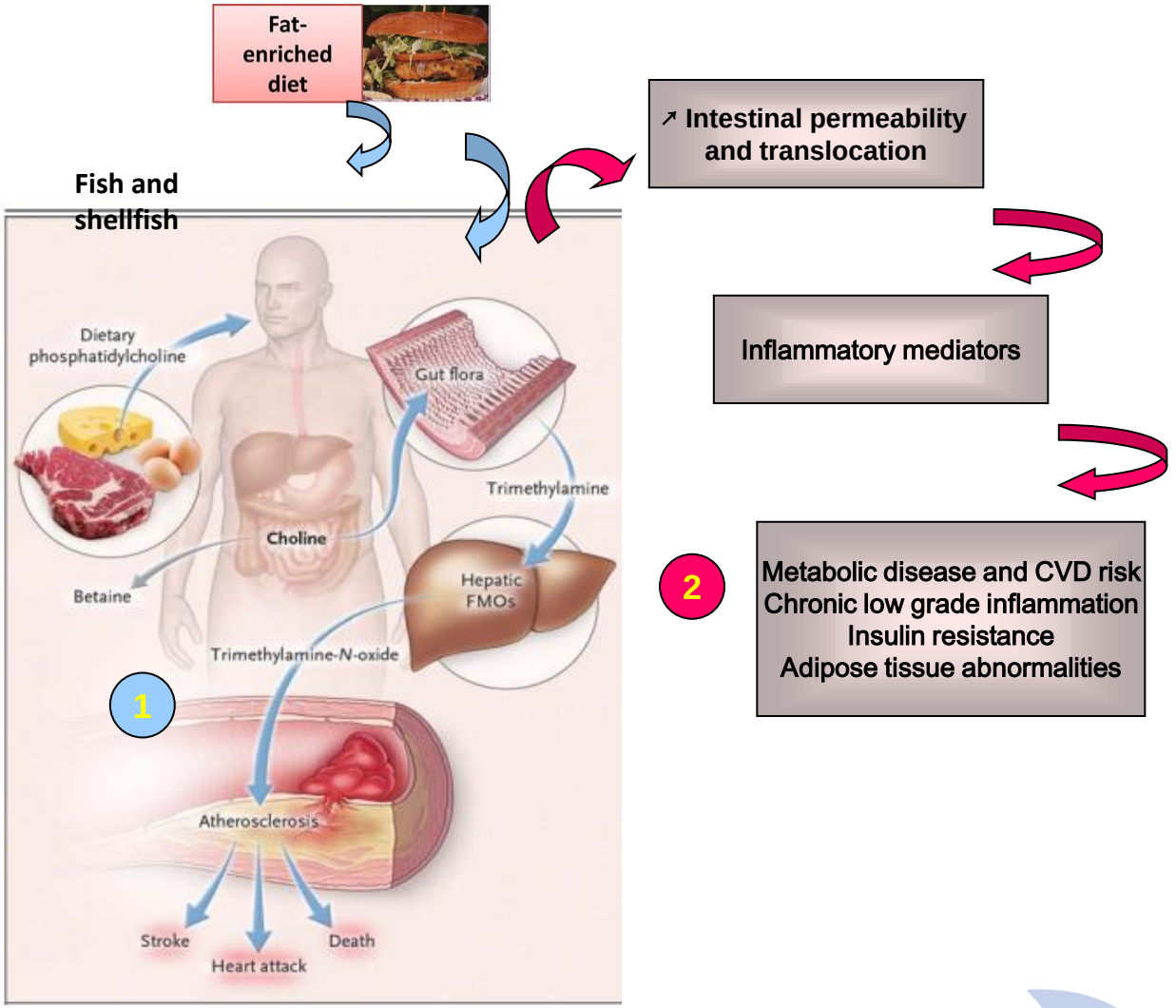


CKD?



Gut Microbiota, TMAO & CVD risks



Adapted from R. Burcelin et al Seminars in Immunology 2012 et Wilson Tang et al, NEJM 2013 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

ICAN TOGETHER

TMAO: a link bewteen diet (choline), microbiota and CVD

4007 patients undergoing elective coronary angiography

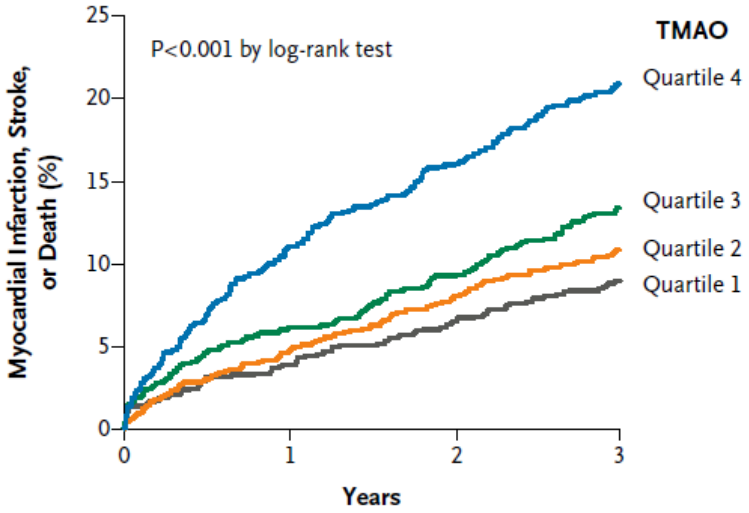
3yr follow up

Table 1. **Baseline Characteristics of the Participants in the Clinical-Outcomes Study, According to Status with Respect to Major Adverse Cardiovascular Events at 3 Years.***

Characteristic	All Participants (N=4007)	Participants without Events (N=3494)	Participants with Events (N=513)	P Value†
Age — yr	63±11	62±11	68±10	<0.001
Male sex — %	64	65	62	0.16
Median TMAO (interquartile range) — μM	3.7 (2.4–6.2)	3.5 (2.4–5.9)	5.0 (3.0–8.8)	<0.001

Older, higher glycemia, % T2D↗ % AHT ↗, MI history

2.5-fold increase in risk



↗ basal TMAO remains an independent factor of CV events after adjusting for traditional risk factors.

Tang *et al.* NEJM 2013

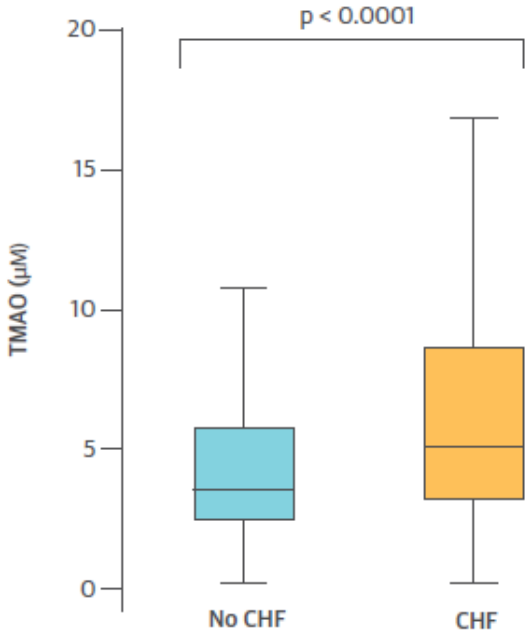
TMAO: prognostic value for patients with Heart Failure

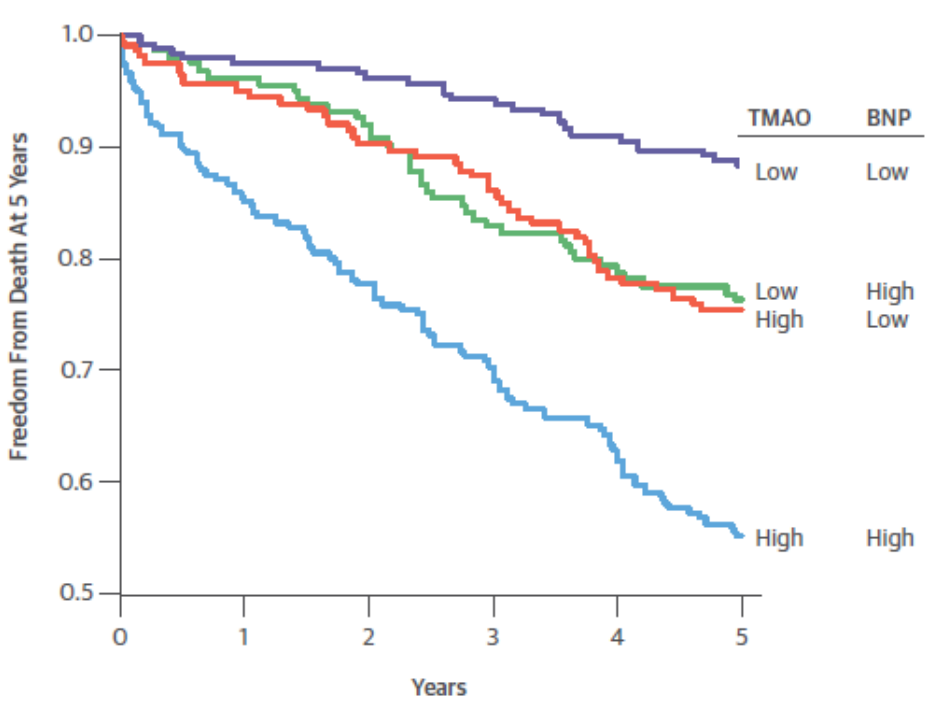
720 patients with stable HF

5yr follow up

TABLE 1 Baseline Characteristics of Heart Failure Cohort (n = 720)

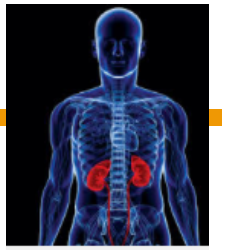
	Overall	TMAO <5 μM	TMAO ≥5 μM	p Value
Age, yrs	66 ± 10	64 ± 11	68 ± 10	<0.001
Male	59	59	59	1.000
Diabetes mellitus	41	31	51	<0.001
Hypertension	78	76	79	0.316
Ischemic etiology	64	63	65	0.673
LV ejection fraction	35 (25-50)	35 (25-51)	40 (25-50)	0.567
Body mass index, kg/m^2	28.4	28.7	28.1	0.298





Tang *et al.* J American College of Cardiology 2014

Emerging data for CKD patients



- CKD patients: incr. TMAO (Tang WHW et al, J Card Fail, 2015)
- Hemodyalisis (1 session): Dec. TMAO (Bain MA, 2006)
- Kidney transplantation: Dec. TMAO (Stubbs JR, JASN. 2015)
- High TMAO: Predictor of all cause mortality (Onopiuk A 2015) or long-term cardiac death or coronary atherosclerosis (Stubbs JR, JASN. 2015)

- ➢ No information on CKD stage of progression
- ➢ No information on food intake consumption

TMAO and Chronic Kidney Disease (2)

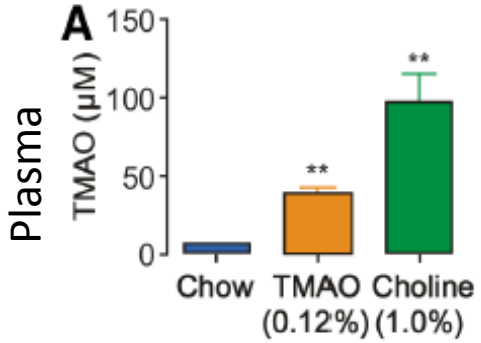
Tang *et al.* 2015

6 weeks

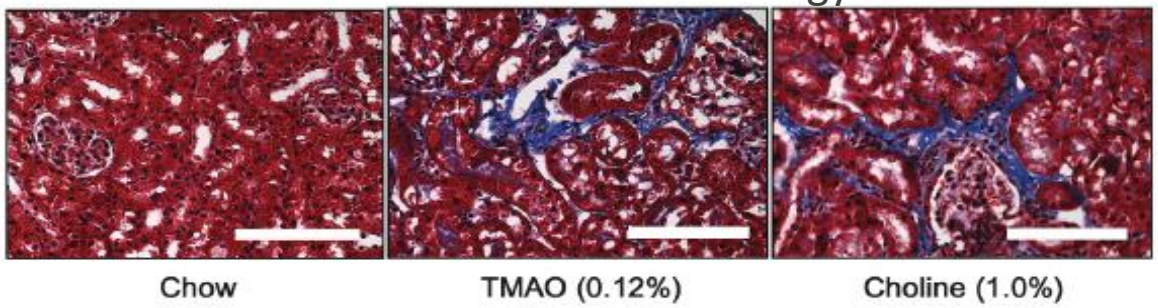
Chow (choline 0,08%)

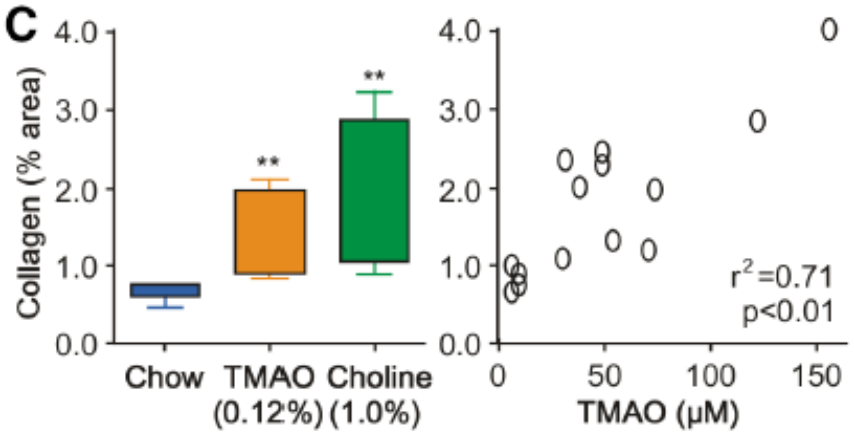
Chow + **TMAO** (0,12%)

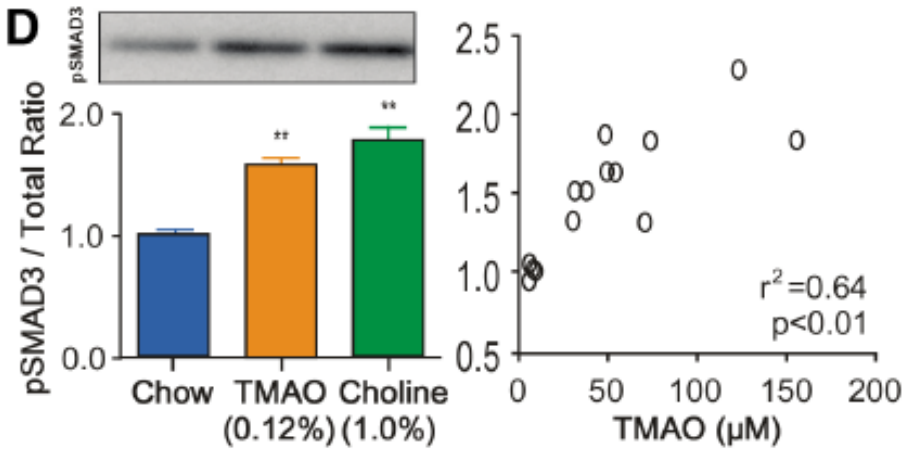
Chow + **Choline** (1%)



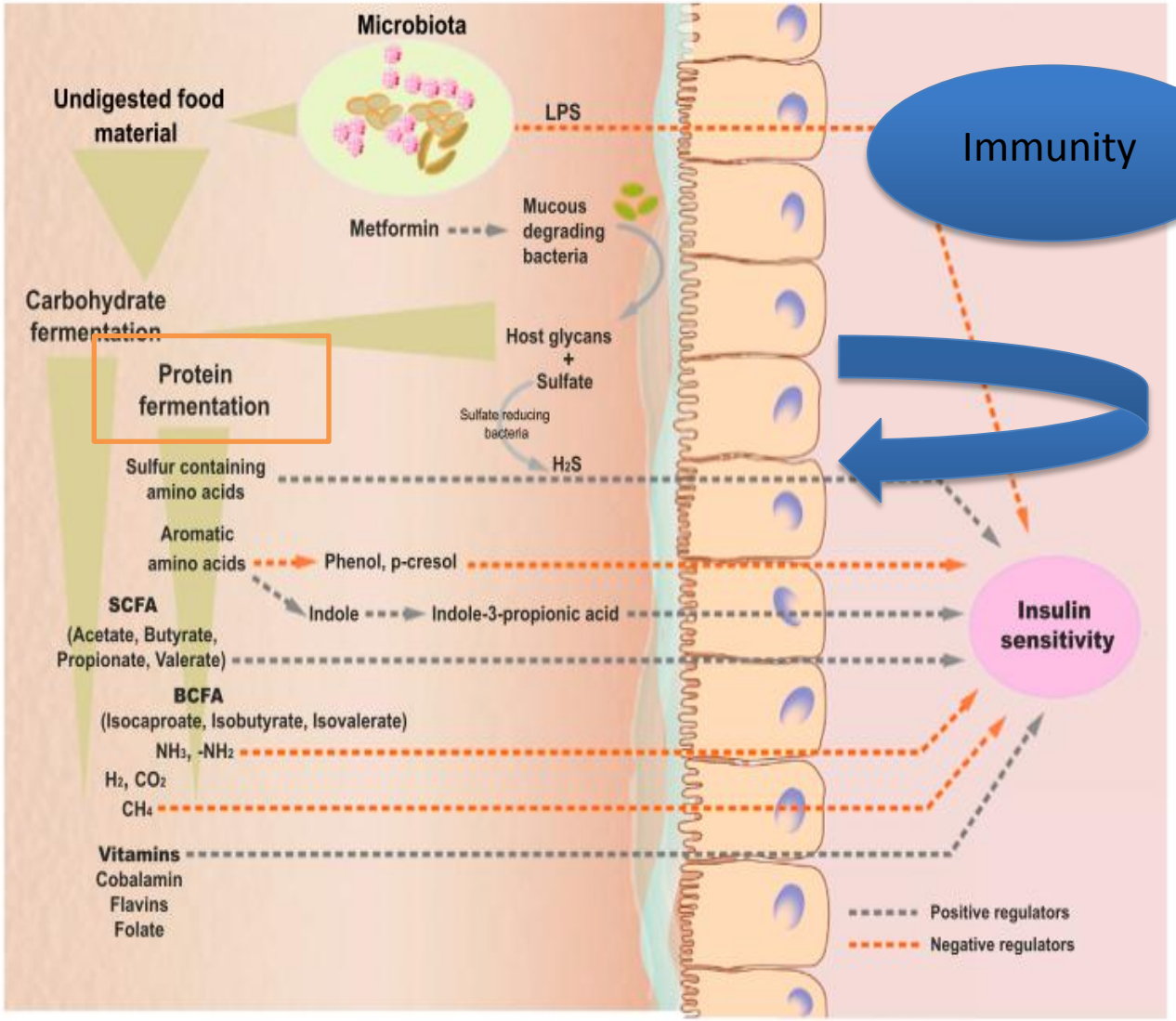
Mason trichrome histology







Many other Metabolites +++ uremic



Intestinal barrier

Two candidates

Indoxyl Sulfate

P Cresol

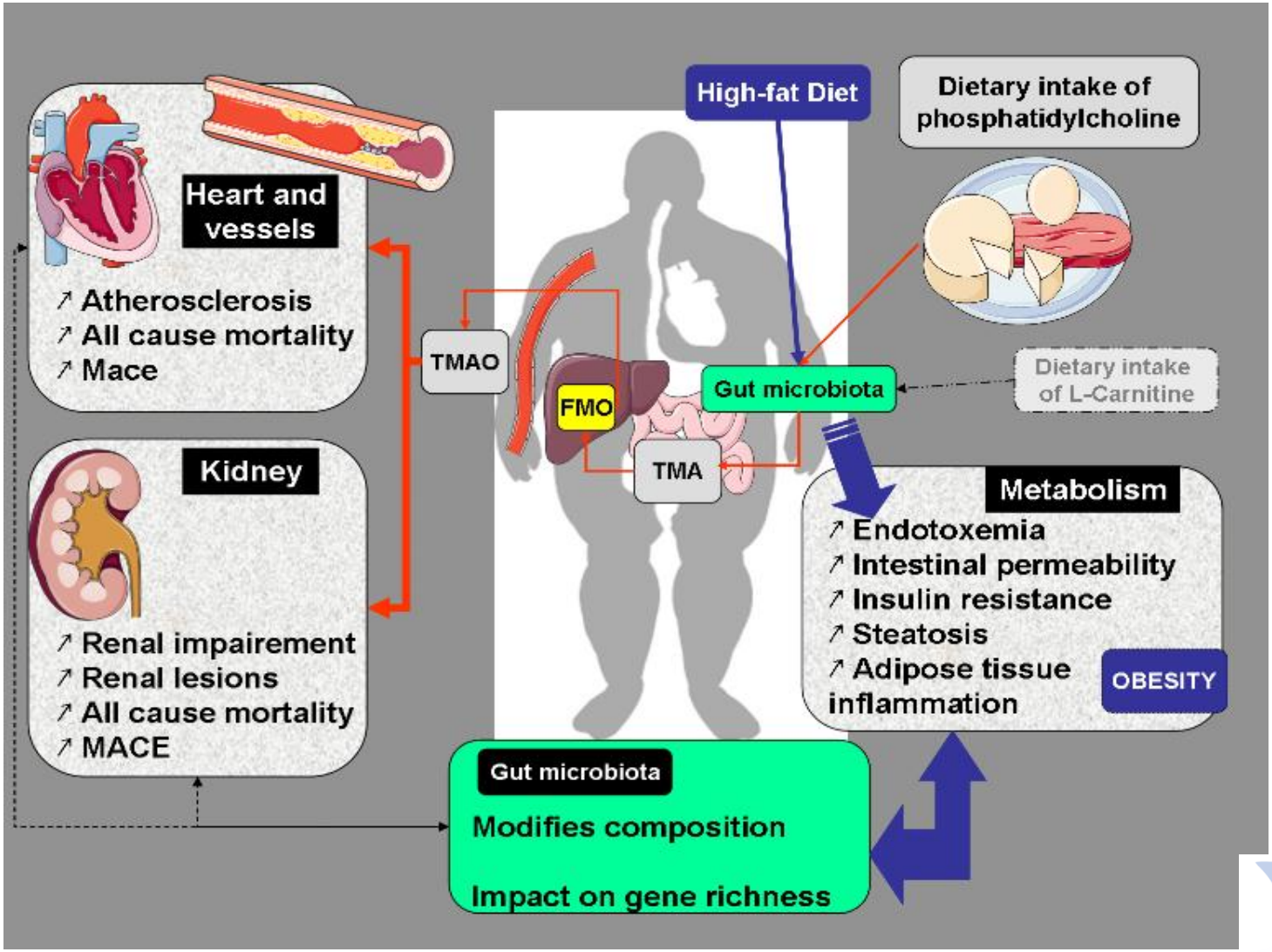
Linked to Kidney function
CKD progression
Mortality (dialysis)

Vascular stfiffness & CVD

Ali Ramezani, and Dominic S. Raj
JASN 2014;25:657-670

Adapted from Khan MT, et al, Cell Metab 2014

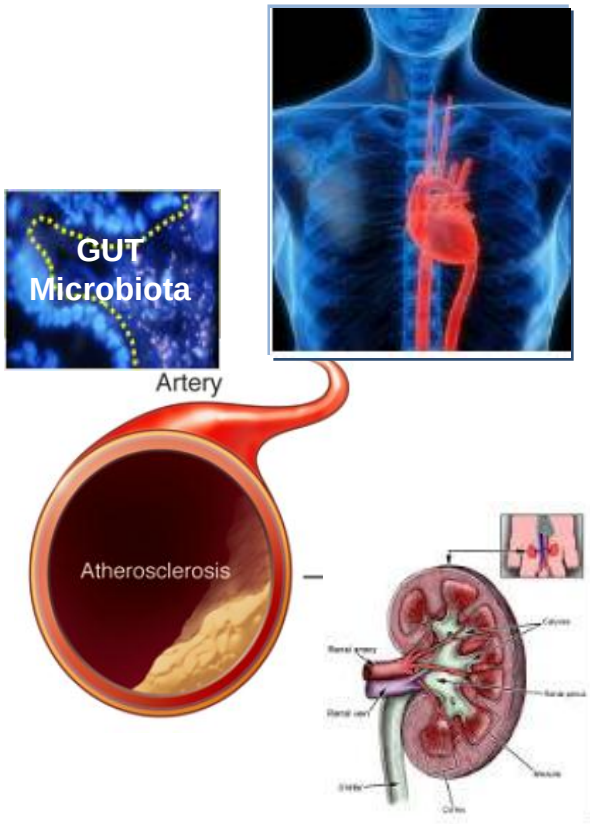
Summary : shared pathway?



Aron-Wisnewsky J and Clément K, Nature Nephr. In press

General conclusions

- Direct link shown between diet, microbiota and CVD, especially in animal models.
- Although mechanisms remain to be explored, different factors of gut microbiota (composition and richness, bacterial function and structural components) are linked with the health of the host.
- Gut microbiota is modifiable, and this can serve as target for improvement of disease.
- THERAPY ? (PRE, PRO BIOTICS, TRANSFER..)

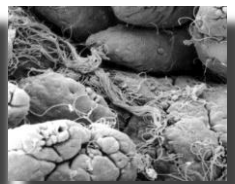


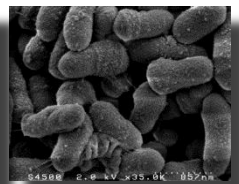

Faecalibacterium prausnitzii

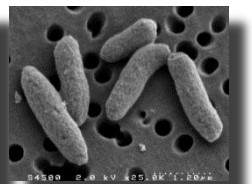

Ruminococcus spp

Photos INRA


Clostridium difficile en caecum souris


Bactéries ancrées dans une Plaque de Peyer, Intestin de souris


Bacteroides dorei


Escherichia coli

ICAN Institute of Cardiometabolism And Nutrition

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Salwa Rizkalla

Aurelie Cotillard

Jean-Daniel Zucker

Edi Prifti

the Musketeers

Carlota Dao

Judith Aron

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Metacardis Community

CommHERE. Communicating European Health Research NETWORK

Agence Nationale de la Recherche ANR

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

UPMC PARIS UNIVERSITAS

DANONE RESEARCH