« LE MICROBIOME »
de découverte en stupéfaction

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Colloque AIPI

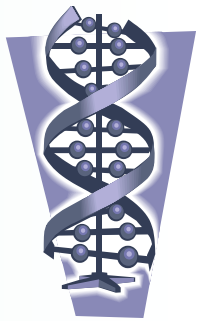
16-18 mai 2016

Menu

- Le tube digestif et les bactéries : bref historique
- Les micro organismes nos symbiontes
- Les analyses métagénomiques ???
- Les gènes qui influencent nos gènes
- L'alimentation qui influence nos bons locataires qui influencent nos gènes
- Le microbiome, l'inflammation et la dépression

Les analyses: historique

- La génétique : analyse de la transmission des caractères héréditaires (19 ième siècle)
- L'ADN = gènes (1950)
- La génomique : analyse des gènes d'un individu, d'une espèce (décodage ARN et ADN) (1970)
- Projet génome humain (1980)
- Les microARN (1993→2003)



Séquençage à haut débit

- Séquencage rapide:
  - « PYROSEQUENCING » (Ronaghi, Nyrën: 1996)
  - “DNA colony sequencing” (Mayer, Farinelli: 1997)
  - “MASSIVE PARALLEL SIGNATURE SEQ.” (Lynx :2000)
  - “PARALLEL PYROSEQUENCING” (2004)
  - SÉQUENÇAGE PAR SYNTHÈSE (Illimina 2005)
- Résultat: baisse dramatique des coûts
  vitesse X par 10,000

La métagénomique

- La métagénomique: analyses de l'ensemble des gènes dans un échantillon de l'environnement : eau, sol, selle, égoux, etc. (2000)
- Appel au « Human International genome consortium » (2001)
- Proposition du Human Metagenomic Project (2002)
- Équipements de séquencage à haut débit (2005)
- Paris 2005 et Toronto (2009) Canada: CMI (2008)
- Financement NIH (2008): 115 M sur 5 ans

Séquenceur: 6 milliards de bases

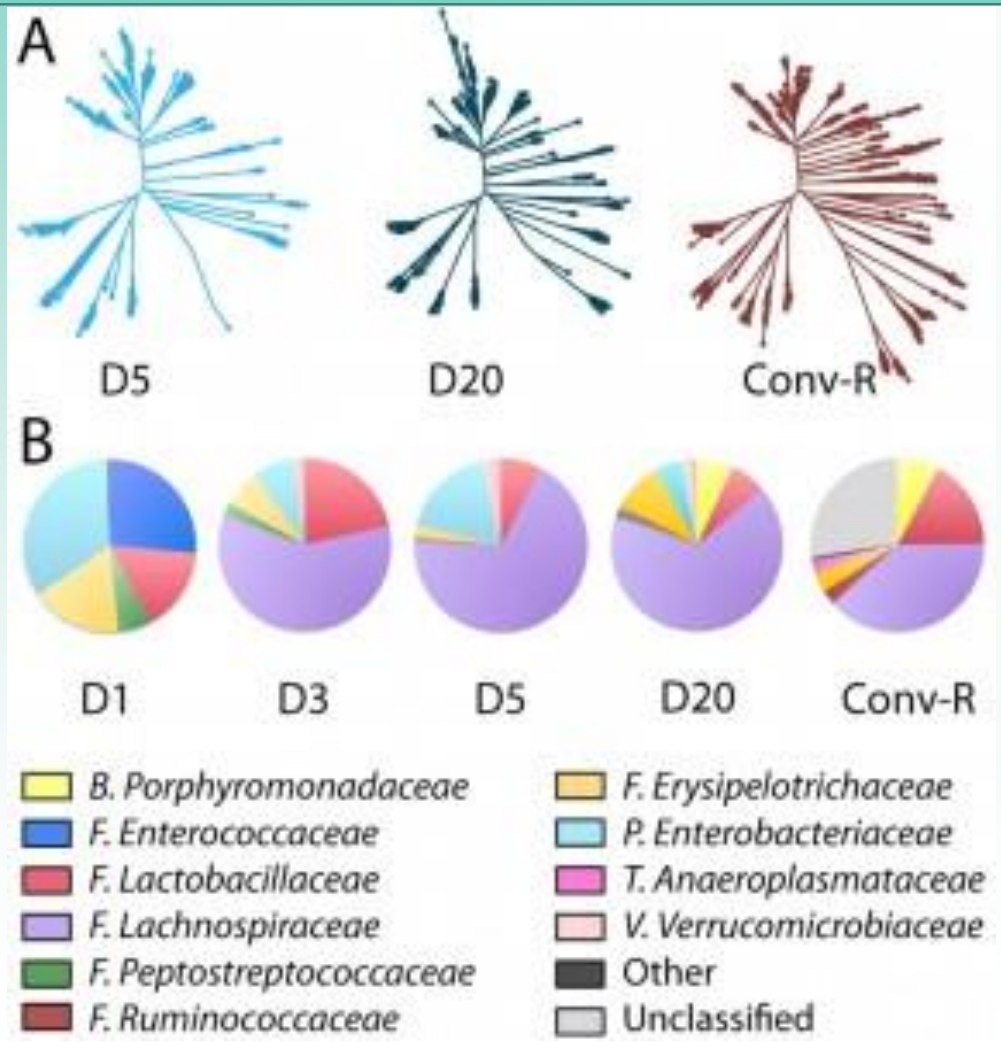
Au Canada : Canadian Microbiome Initiative

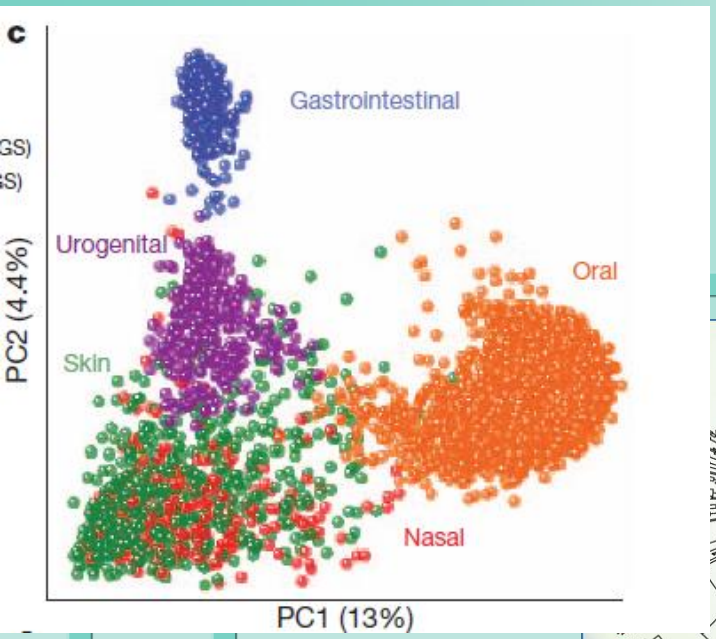
Études HMP (03/2014)

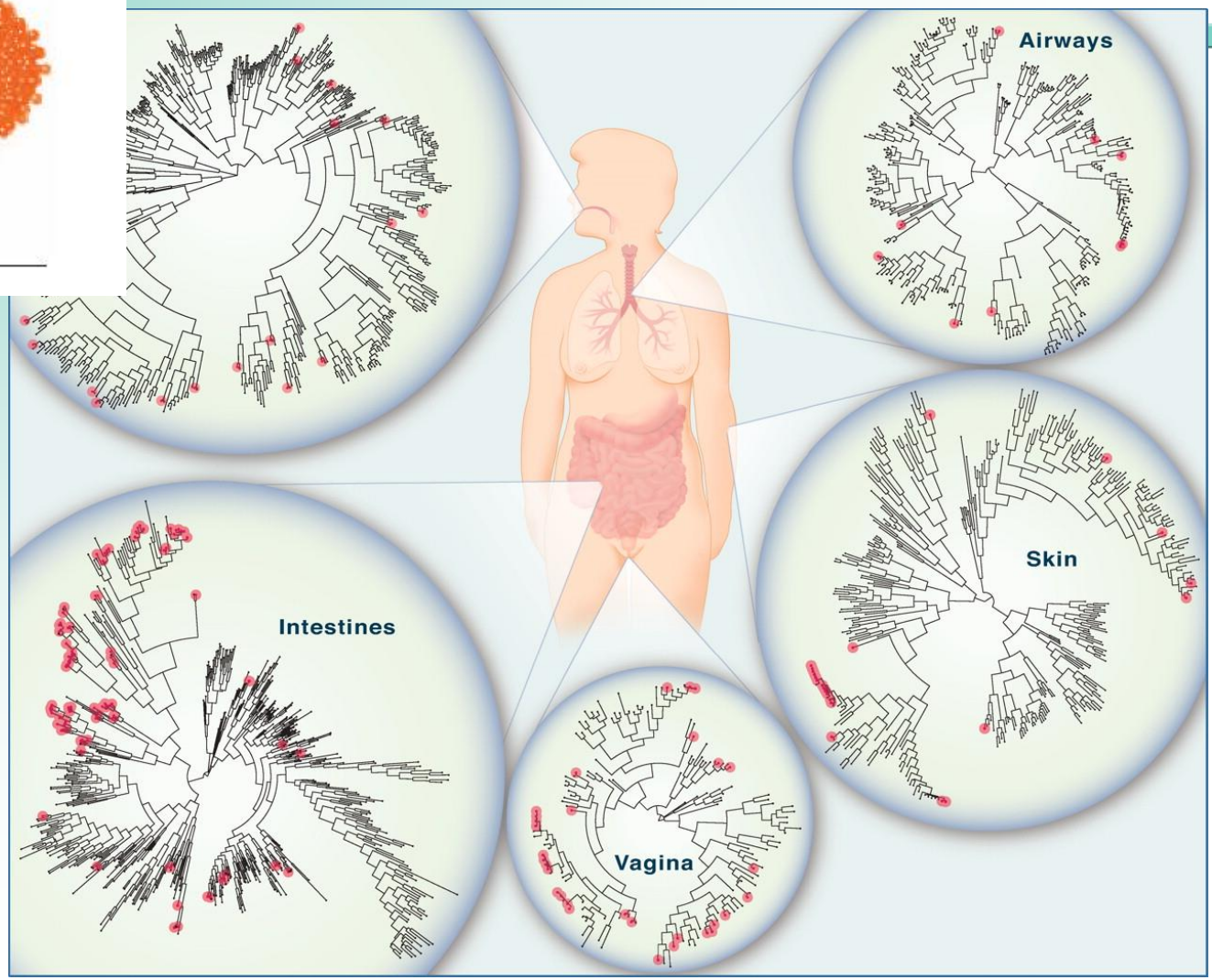
Category	All projects
Airways	144
Blood	70
Eye	1
Gastrointestinal tract	717
Gut	28
Heart	2
Liver	1
Lymph Node	1
Nose	2
Oral	434
Oral Cavity	11
Oral cavity- mouth	1
Skin	290
Urogenital tract	356
Wound	4
Other	611
All Strains	2673

The Economist
The Catholic church's unholy mess
Paul Ryan: the man with the plan
Generation Xhausted
China, victim of the Olympics?
On the origin of specie
AUGUST 18TH–24TH 2012
Economist.com
Microbes maketh man
How 90% of the cells in your body are bacteria, the benefits of faecal transplants, and other things you would rather not know before breakfast

On étudie les gènes microbiens par ordinateurs




c
Gastrointestinal
Urogenital
Oral
Skin
Nasal
PC2 (4.4%)
PC1 (13%)


Airways
Skin
Intestines
Vagina

statistically significant co-abundance groups (Supplementary Notes). The dominant genera in these CAGs were *Bacteroides*, *Prevotella*,

associated health to long-stay-associated frailty (plot 1A–4A, and 1B–4B), which were examined with reference to health correlations

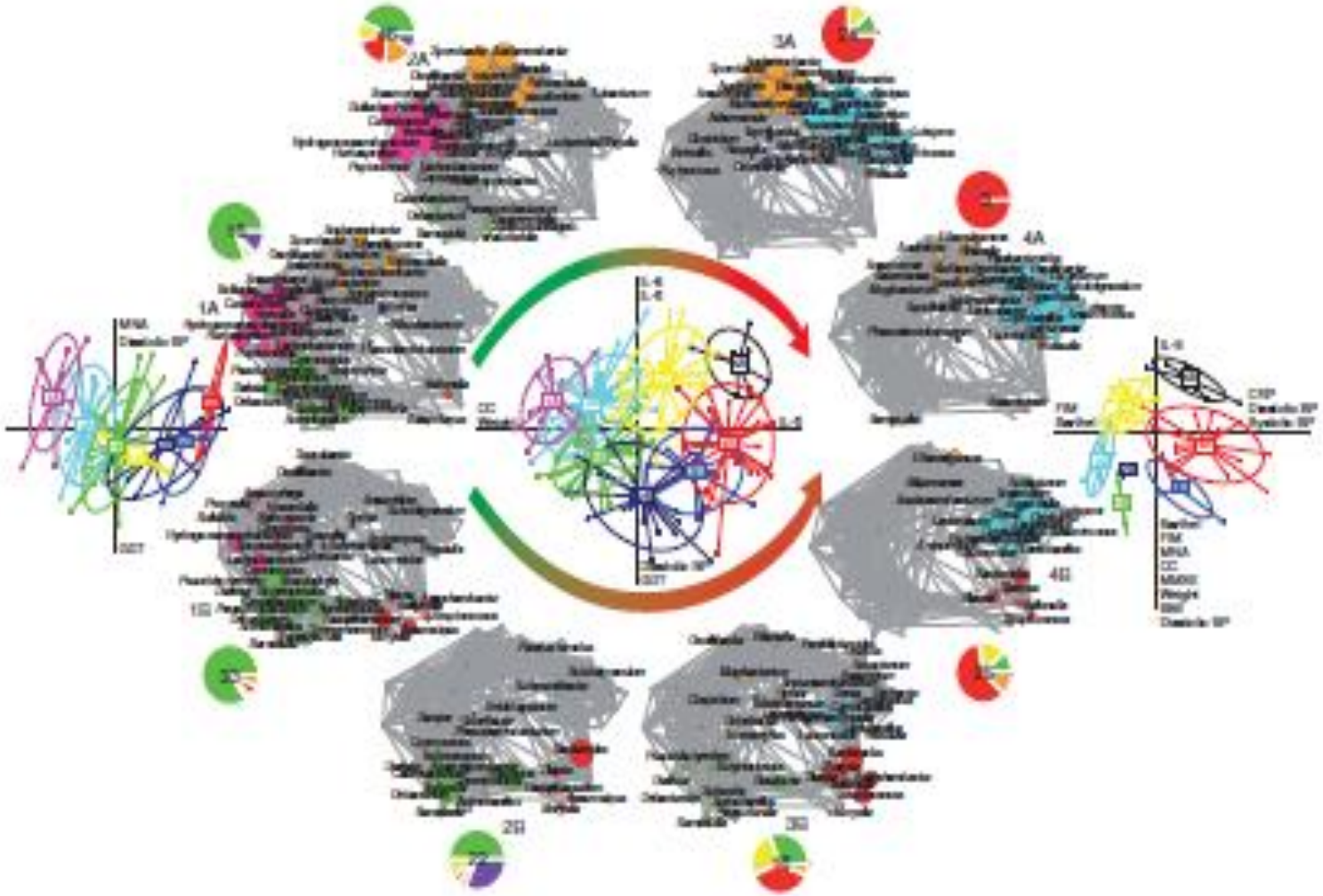
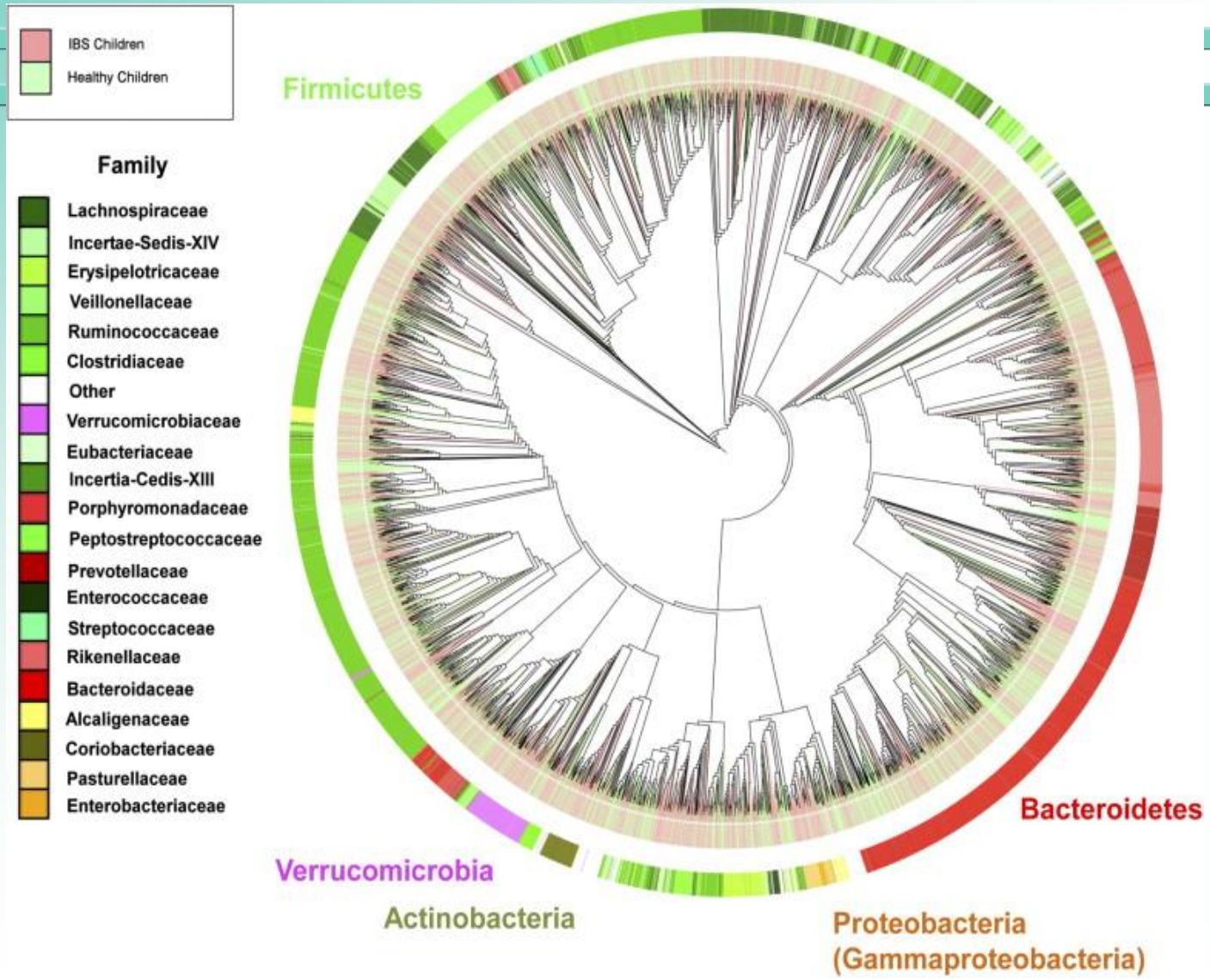
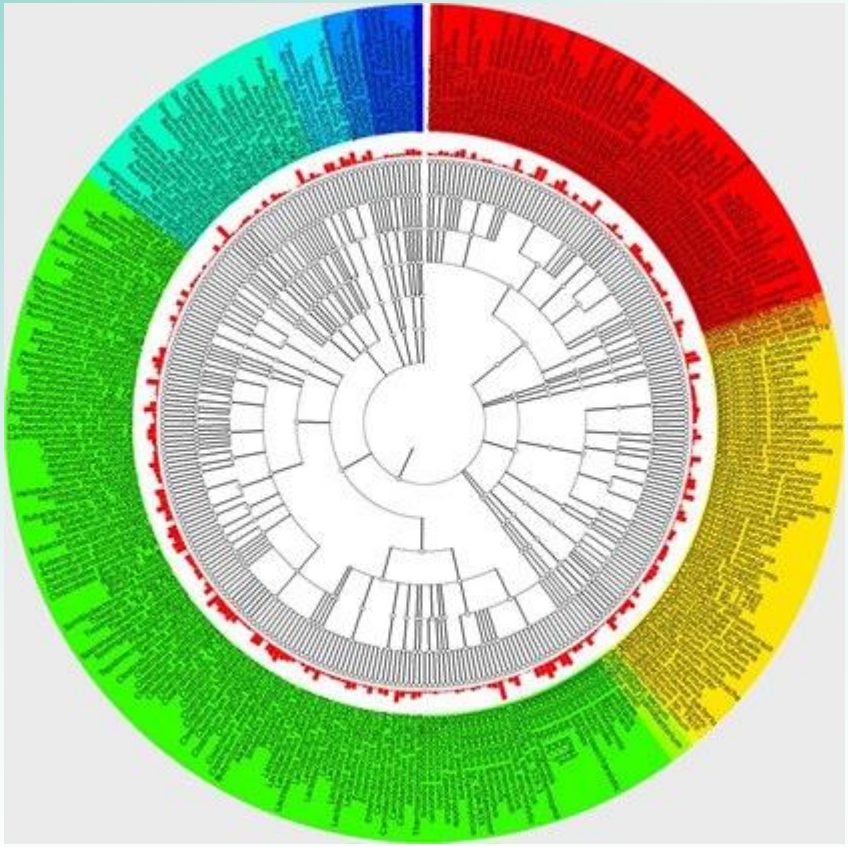


Figure 4 | Transition in microbiota composition across residence locations mirrored by changes in health indices. The PCoA plots show 8 groups of subjects defined by unweighted UniFrac microbiota analysis of community subjects (left), the whole cohort (centre), and long-stay subjects (right). The main circle shows the Wiggam plots corresponding to the 8 groups from whole-cohort analysis, in which discs indicate genus over-abundance relative to background. The pie charts show residence location proportions (colour coded as in Fig. 1c) and number of subjects per subject group. Curved arrows indicate transition from health (green) to frailty (red). FIM, functional independence measure; MNA, mini nutritional assessment; GDS, geriatric depression test; CC, calf circumference; CRP, C-reactive protein; IL, interleukin; BP, blood pressure; MMSE, mini-mental state examination.

One exprime les espèces en rosettes de couleurs



Plus on est en santé plus y en a



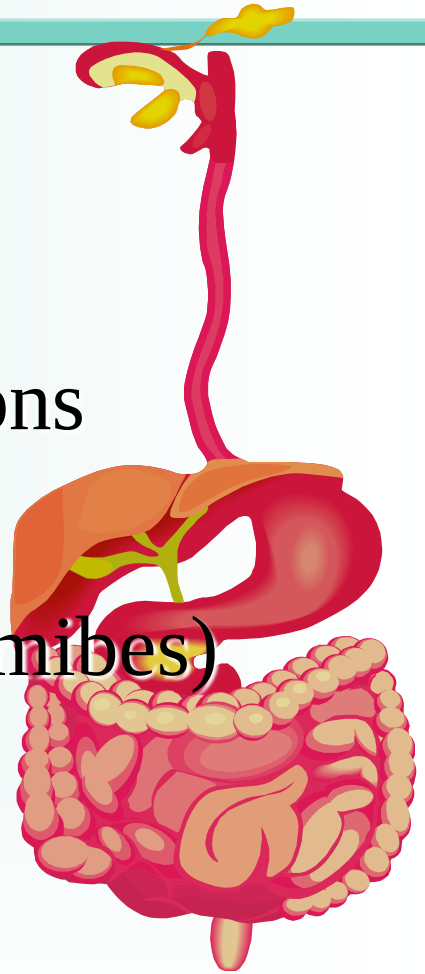
Les microbes qui nous habitent

<u>Dans le tube digestif:</u>

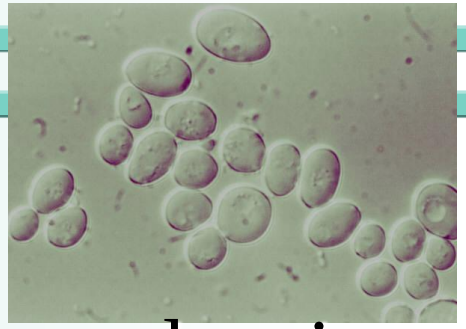
- Bactéries : 100 trillions
- Virus bactériophages: 1000 trillions
- Champignons et levure:
- Parasites : vers et protozoaires (amibes)

<u>Sur la peau:</u> les ongles, les cheveux etc

<u>Ils sont partout :</u> Le placenta, l'urine etc….



Le tube digestif et les microbes



- Premier organe cellulaire
- Colonisé par des micro organismes depuis plus de 1,500 millions d'années en partenariat (mitochondrie)
- Contient 80% du système immunitaire qui :
  - Éduquent nos défenses (modèle des souris axéniques)
  - Nous permettent de digérer (ex.: le gluten)
  - Essentiels pour demeurer en santé !!!!?

Symbionte: définition

- Être vivant qui vit dans un autre pour un bénéfice mutuel (symbiose)
  - Plantes et rhizomes
  - Crabe Hermite et l'anémone
  - Insectes et bactéries
  - Mon voisin et son épouse
  - Les herbivores et les bactéries du rumen

QU'A-T-ON DÉCOUVERT?

- 150-300 Fois plus de matériel génétique dans l'intestin que nos propres gènes (6M de nouveau gènes)
  - >600 nouvelles espèces (+ de 1000 au total)
- Que nos amis intérieurs vivent en symbiose avec nous (parasites inclus) La symbiose remonte au début de la vie.
- Que la nourriture et les microorganis
  fournissent du matériel génétique qu
  l'expression de nos propres gènes (l'é
  - Ex.: le riz (et son microARN)

Découvertes

- Mars 2010 : 1 de 3 combinaisons retrouvées chez les personnes en bonne santé
- Plusieurs espèces seraient intra parasitaires
  - Modèle de la souris par ré-introduction
  - Essais humains avec œufs de Trichuris (2003)
- Impliqué dans l'obésité (ex.: Akermansia)
- Le microbiome est « différent » dans plusieurs maladies et cancers

Microbiome et obésité

Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Science 6 September 2013:
Vol. 341 no. 6150
DOI: 10.1126/science.1241214

- RESEARCH ARTICLE

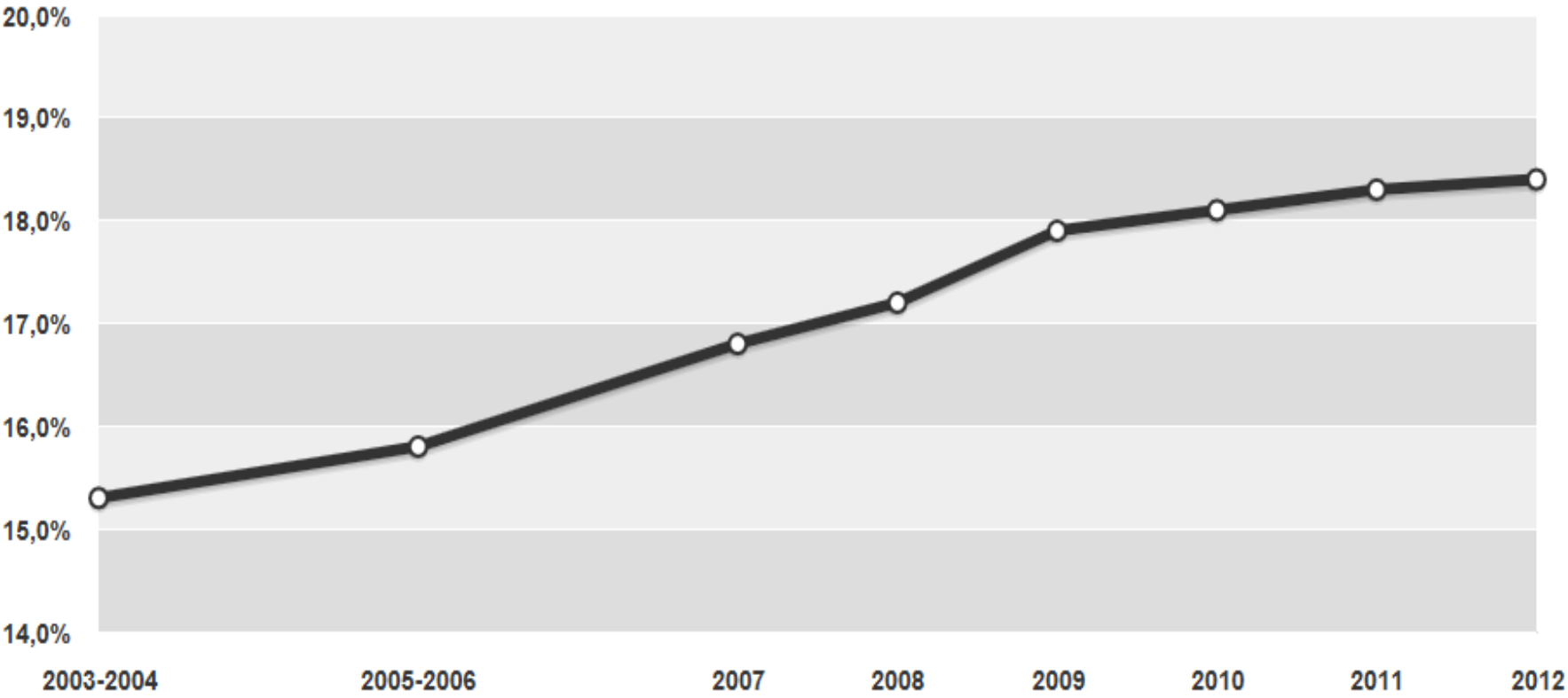
Gut Microbiota from Twins Discordant for Obesity Modulate Metabolism in Mice

Vanessa K. Ridaura[1], Jeremiah J. Faith[1], Federico E. Rey[1], Jiye Cheng[1], Alexis E. Duncan[2,3], Andrew L. Kau[1], Nicholas W. Griffin[1], Vincent Lombard[4], Bernard Henrissat[4,5], James R. Bain[6,7,8], Michael J. Muehlbauer[6], Olga Ilkayeva[6], Clay F. Semenkovich[9], Katsuhiko Funai[9], David K. Hayashi[10], Barbara J. Lyle[11], Margaret C. Martini[11], Luke K. Ursell[12], Jose C. Clemente[12], William Van Treuren[12], William A. Walters[13], Rob Knight[12,14,15], Christopher B. Newgard[6,7,8], Andrew C. Heath[2], Jeffrey I. Gordon[1,*]

Source : Statistique Canada

Obésité, 2003 à 2012

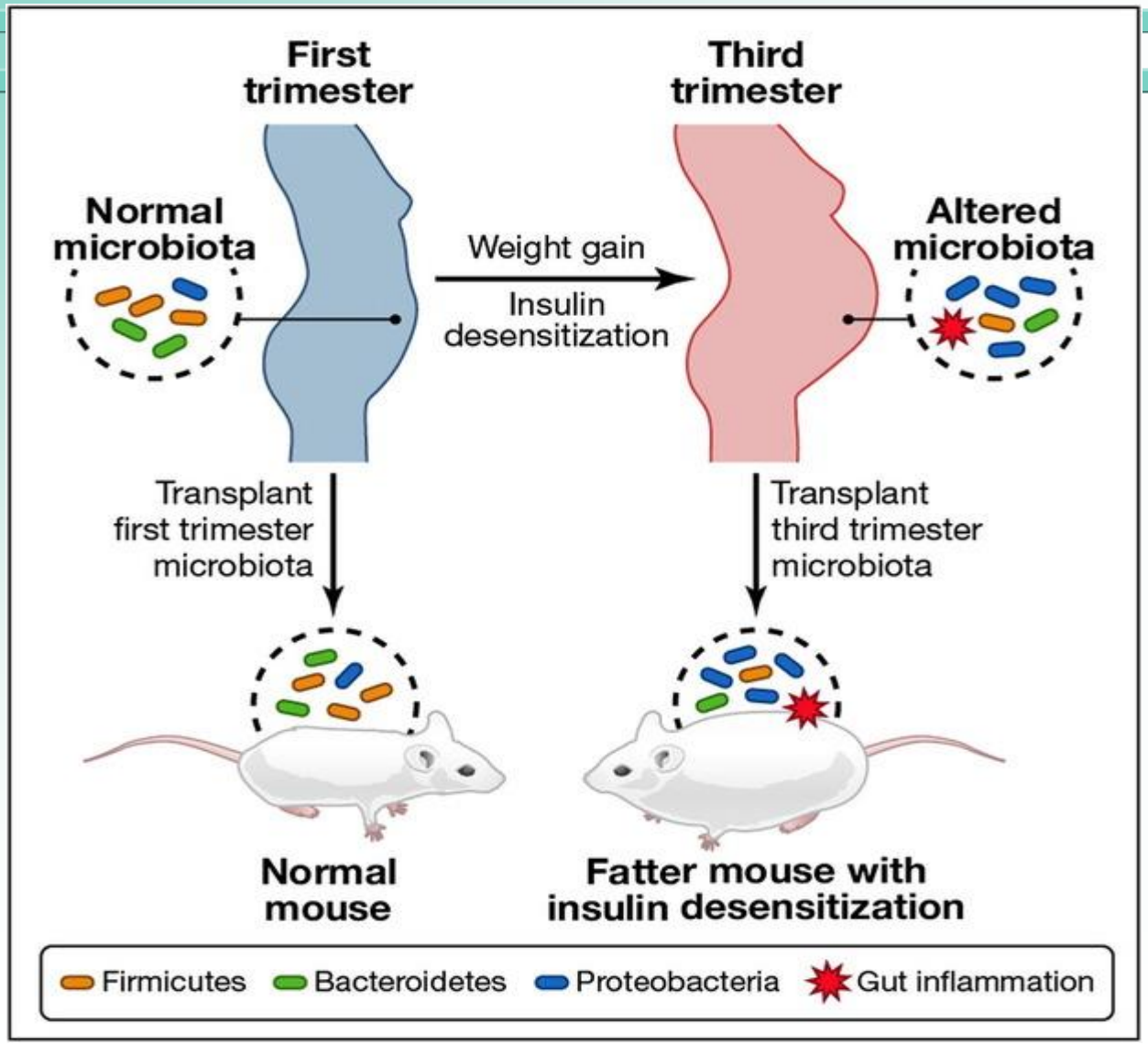
Affichez jusqu'à trois provinces ou territoires en les sélectionnant (recliquez pour désélectionner). Vous pouvez également AJOUTER une ville pour trouver les résultats de sa région sanitaire à l'aide du champs de recherche ci-dessous. Au moins trois ans de données doivent être disponibles pour voir apparaître les résultats des tendances sur le graphique.



Microbiome et obésité

- Étude des jumeaux humains identiques discordant
  - La transplantation de selles du jumeau:
    - » Obèse donne des souris obèses
    - » Maigre donne des souris maigres

Le microbiome et la grossesse



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 25, 2013 VOL. 368 NO. 17

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

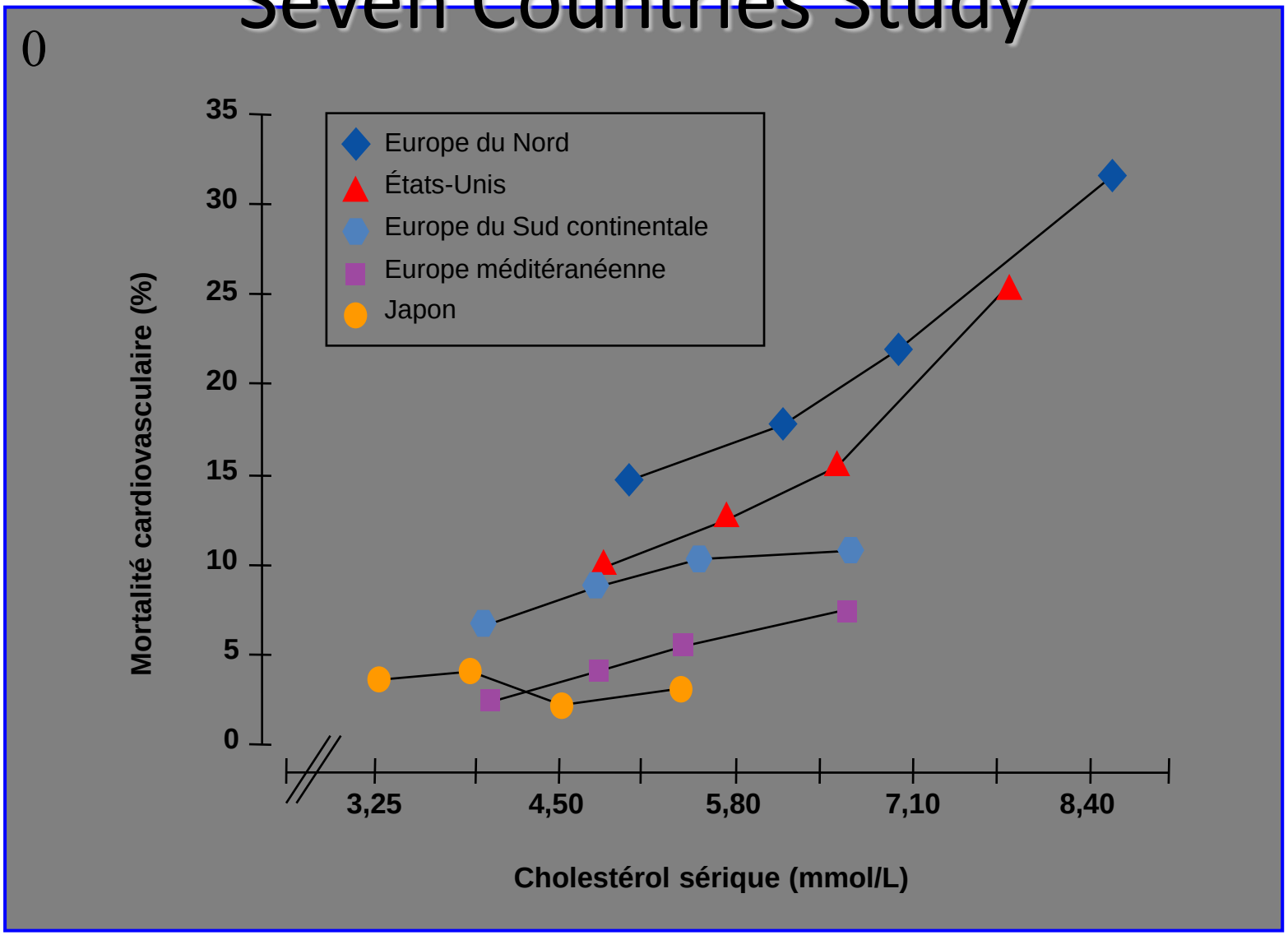
W.H. Wilson Tang, M.D., Zeneng Wang, Ph.D., Bruce S. Levison, Ph.D., Robert A. Koeth, B.S., Earl B. Britt, M.D., Xiaoming Fu, M.S., Yuping Wu, Ph.D., and Stanley L. Hazen, M.D., Ph.D.

Viande rouge et cancer

(4007 personnes et suivi X 3 ans)

- TMAO: triméthylamide-N-oxide
  - Substance pro-inflammatoire
  - Carcinogène connu (néo du colon)
- Bactéries : transformation de la carnitine en TMAO via la phosphatidylcholine
- -Carnivores: TMAO élevé = risque élevé de SCA et de cancer de l'intestin
- -Végétariens: peu ou pas de phosphatidylcholine
- -Végé -> Carni: montre une augmentation de la phosphaditylcholine avec l'arrivée de bactéries différentes

Mortalité cardiovasculaire sur 25 ans
Seven Countries Study



ORIGINAL INVESTIGATION

Meat Intake and Mortality

A Prospective Study of Over Half a Million People

Rashmi Sinha, PhD; Amanda J. Cross, PhD; Barry I. Graubard, PhD; Michael F. Leitzmann, MD, DrPH; Arthur Schatzkin, MD, DrPH

Background: High intakes of red or processed meat may increase the risk of mortality. Our objective was to determine the relations of red, white, and processed meat intakes to risk for total and cause-specific mortality.

Methods: The study population included the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) Diet and Health Study cohort of half a million people aged 50 to 71 years at baseline. Meat intake was estimated from a food frequency questionnaire administered at baseline. Cox proportional hazards regression models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) within quintiles of meat intake. The covariates included in the models were age, education, marital status, family history of cancer (yes/no) (cancer mortality only), race, body

in the highest vs lowest quintile of red (HR, 1.31 [95% CI, 1.27-1.35], and HR, 1.36 [95% CI, 1.30-1.43], respectively) and processed meat (HR, 1.16 [95% CI, 1.12-1.20], and HR, 1.25 [95% CI, 1.20-1.31], respectively) intakes had elevated risks for overall mortality. Regarding cause-specific mortality, men and women had elevated risks for cancer mortality for red (HR, 1.22 [95% CI, 1.16-1.29], and HR, 1.20 [95% CI, 1.12-1.30], respectively) and processed meat (HR, 1.12 [95% CI, 1.06-1.19], and HR, 1.11 [95% CI 1.04-1.19], respectively) intakes. Furthermore, cardiovascular disease risk was elevated for men and women in the highest quintile of red (HR, 1.27 [95% CI, 1.20-1.35], and HR, 1.50 [95% CI, 1.37-1.65], respectively) and processed meat (HR, 1.09 [95% CI, 1.03-1.15], and HR, 1.38 [95% CI, 1.26-1.51], respectively) intakes. When comparing the highest with

Table 2. Multivariate Analysis for Red, White, and Processed Meat Intake and Total and Cause-Specific Mortality in Men in the National Institutes of Health–AARP Diet and Health Study[a]

Mortality in Men (n=322 263)	Quintile					*P* Value for Trend
	Q1	Q2	Q3	Q4	Q5	
		Red Meat Intake[b]				
All mortality						
Deaths	6437	7835	9366	10 988	13 350	
Basic model[c]	1 [Reference]	1.07 (1.03-1.10)	1.17 (1.13-1.21)	1.27 (1.23-1.31)	1.48 (1.43-1.52)	<.001
Adjusted model[d]	1 [Reference]	1.06 (1.03-1.10)	1.14 (1.10-1.18)	1.21 (1.17-1.25)	1.31 (1.27-1.35)	<.001
Cancer mortality						
Deaths	2136	2701	3309	3839	4448	
Basic model[c]	1 [Reference]	1.10 (1.04-1.17)	1.23 (1.16-1.29)	1.31 (1.24-1.39)	1.44 (1.37-1.52)	<.001
Adjusted model[d]	1 [Reference]	1.05 (0.99-1.11)	1.13 (1.07-1.20)	1.18 (1.12-1.25)	1.22 (1.16-1.29)	<.001
CVD mortality						
Deaths	1997	2304	2703	3256	3961	
Basic model[c]	1 [Reference]	1.02 (0.96-1.08)	1.10 (1.04-1.17)	1.24 (1.17-1.31)	1.44 (1.37-1.52)	<.001
Adjusted model[d]	1 [Reference]	0.99 (0.96-1.09)	1.08 (1.02-1.15)	1.18 (1.12-1.26)	1.27 (1.20-1.35)	<.001
Mortality from injuries and sudden deaths						
Deaths	184	216	228	280	343	
Basic model[c]	1 [Reference]	1.02 (0.84-1.24)	0.97 (0.80-1.18)	1.09 (0.90-1.31)	1.24 (1.03-1.49)	.01
Adjusted model[d]	1 [Reference]	1.06 (0.86-1.29)	1.01 (0.83-1.24)	1.14 (0.94-1.39)	1.26 (1.04-1.54)	.008
All other deaths						
Deaths	1268	1636	1971	2239	2962	
Basic model[c]	1 [Reference]	1.13 (1.05-1.22)	1.25 (1.17-1.35)	1.33 (1.24-1.42)	1.68 (1.57-1.80)	<.001
Adjusted model[d]	1 [Reference]	1.17 (1.09-1.26)	1.28 (1.19-1.38)	1.34 (1.25-1.44)	1.58 (1.47-1.70)	<.001

	White Meat Intake[e]					
All mortality						
Deaths	12 521	10 442	9359	8444	7210	
Basic model[c]	1 [Reference]	0.83 (0.81-0.85)	0.77 (0.75-0.79)	0.74 (0.72-0.76)	0.74 (0.72-0.76)	<.001
Adjusted model[d]	1 [Reference]	0.92 (0.90-0.95)	0.90 (0.88-0.93)	0.90 (0.88-0.93)	0.92 (0.89-0.94)	<.001
Cancer mortality						
Deaths	4424	3647	3203	2830	2329	
Basic model[c]	1 [Reference]	0.82 (0.79-0.86)	0.74 (0.71-0.78)	0.71 (0.67-0.74)	0.68 (0.65-0.72)	<.001
Adjusted model[d]	1 [Reference]	0.91 (0.87-0.95)	0.87 (0.83-0.91)	0.85 (0.81-0.90)	0.84 (0.80-0.88)	<.001
CVD mortality						
Deaths	3521	3015	2771	2578	2336	
Basic model[c]	1 [Reference]	0.85 (0.81-0.89)	0.81 (0.77-0.85)	0.81 (0.77-0.85)	0.86 (0.81-0.90)	<.001
Adjusted model[d]	1 [Reference]	0.96 (0.91-1.00)	0.96 (0.91-1.01)	0.99 (0.94-1.04)	1.05 (1.00-1.11)	.009
Mortality from injuries and sudden deaths						
Deaths	333	266	249	219	184	
Basic model[c]	1 [Reference]	0.81 (0.69-0.95)	0.78 (0.66-0.93)	0.73 (0.62-0.87)	0.71 (0.59-0.85)	<.001
Adjusted model[d]	1 [Reference]	0.89 (0.76-1.05)	0.90 (0.76-1.06)	0.86 (0.72-1.03)	0.85 (0.70-1.02)	.11
All other deaths						
Deaths	2775	2206	1948	1722	1425	
Basic model[c]	1 [Reference]	0.79 (0.75-0.83)	0.72 (0.68-0.76)	0.68 (0.64-0.73)	0.67 (0.63-0.72)	<.001
Adjusted model[d]	1 [Reference]	0.90 (0.85-0.95)	0.88 (0.83-0.93)	0.86 (0.81-0.92)	0.86 (0.80-0.92)	<.001

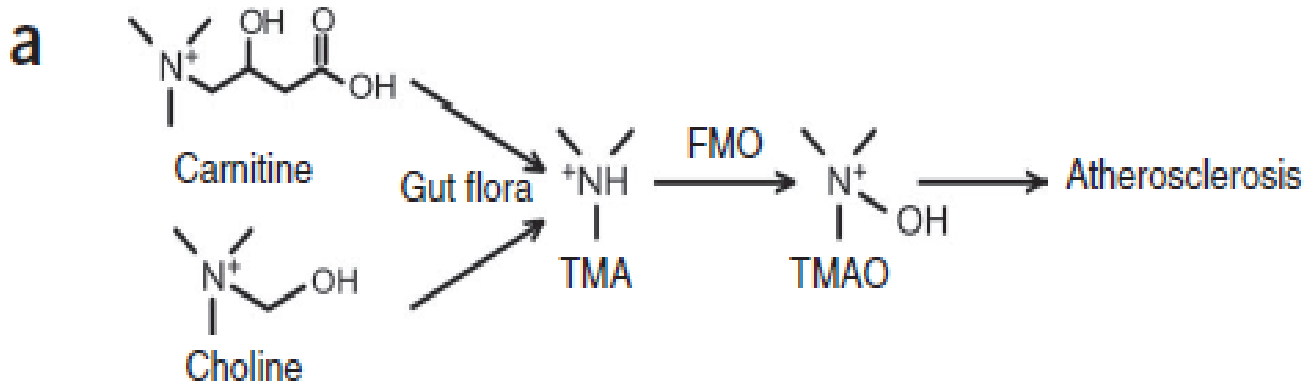
ARTICLES

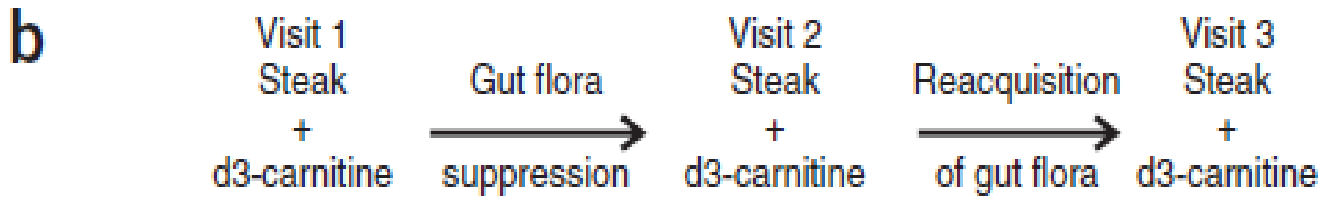
nature medicine

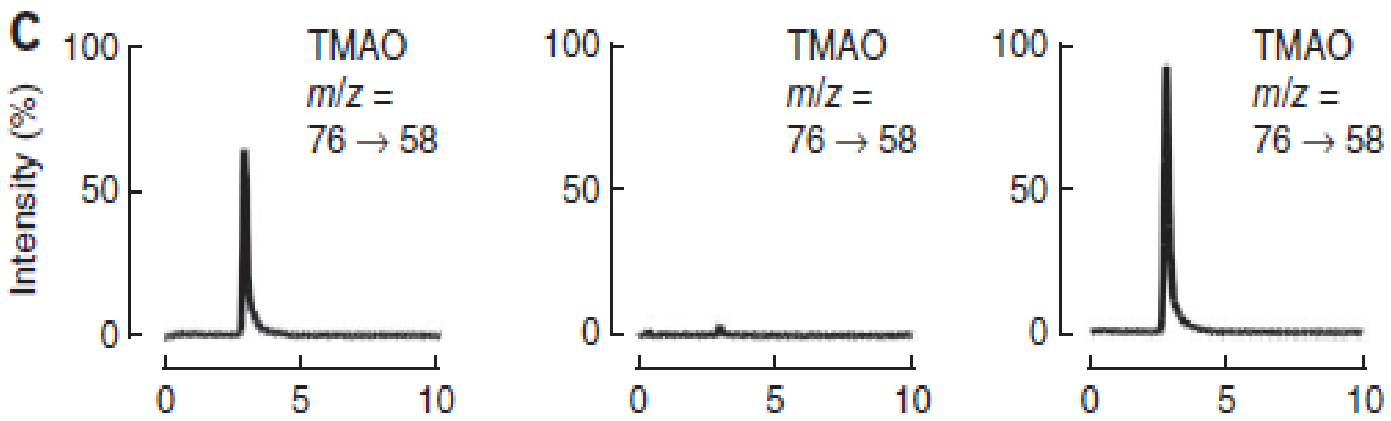
Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis

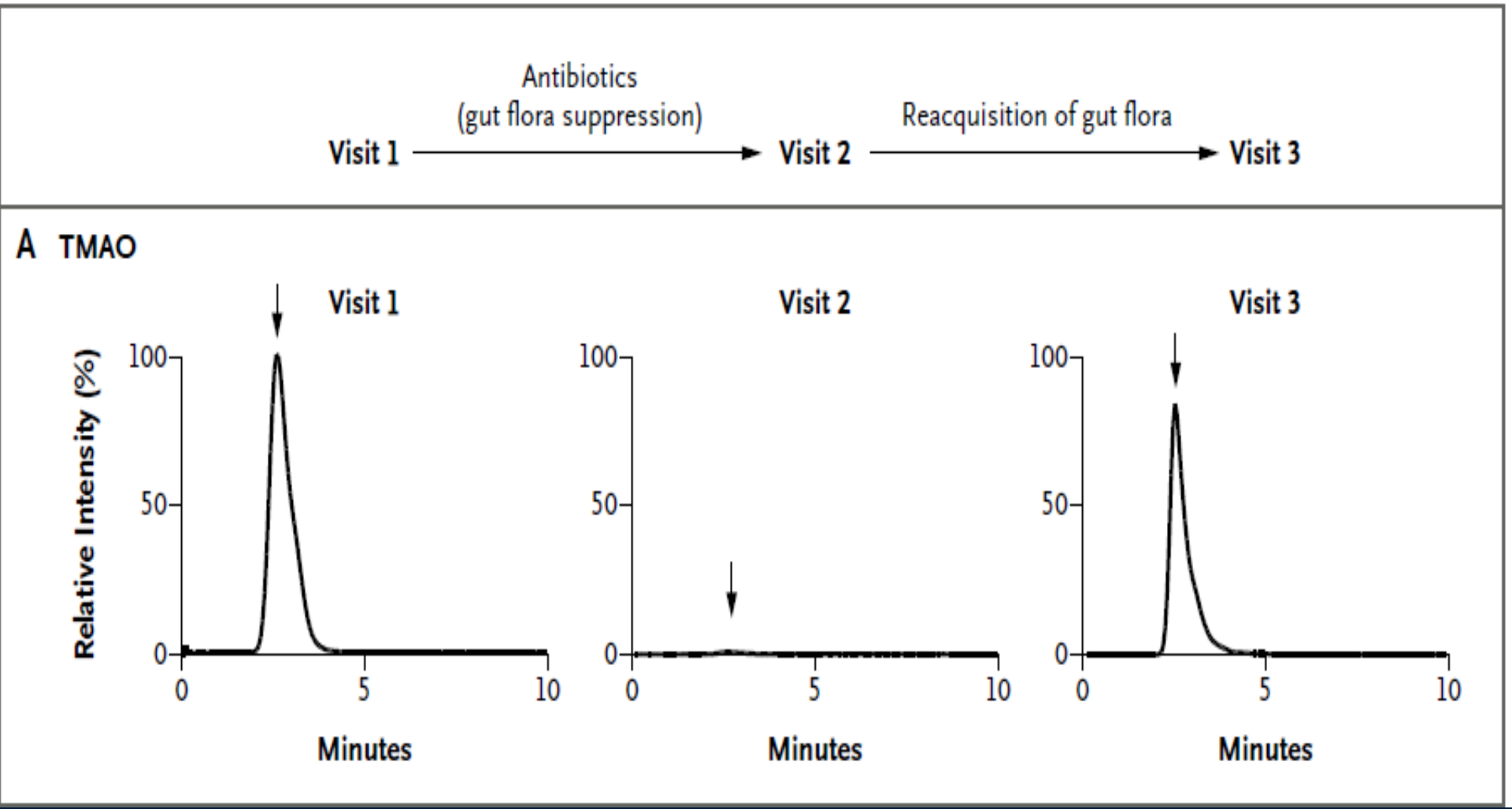
Robert A Koeth[1,2], Zeneng Wang[1,2], Bruce S Levison[1,2], Jennifer A Buffa[1,2], Elin Org[3], Brendan T Sheehy[1], Earl B Britt[1,2], Xiaoming Fu[1,2], Yuping Wu[4], Lin Li[1,2], Jonathan D Smith[1,2,5], Joseph A DiDonato[1,2], Jun Chen[6], Hongzhe Li[6], Gary D Wu[7], James D Lewis[6,8], Manya Warrier[9], J Mark Brown[9], Ronald M Krauss[10], W H Wilson Tang[1,2,5], Frederic D Bushman[5], Aldons J Lusis[3] & Stanley L Hazen[1,2,5]

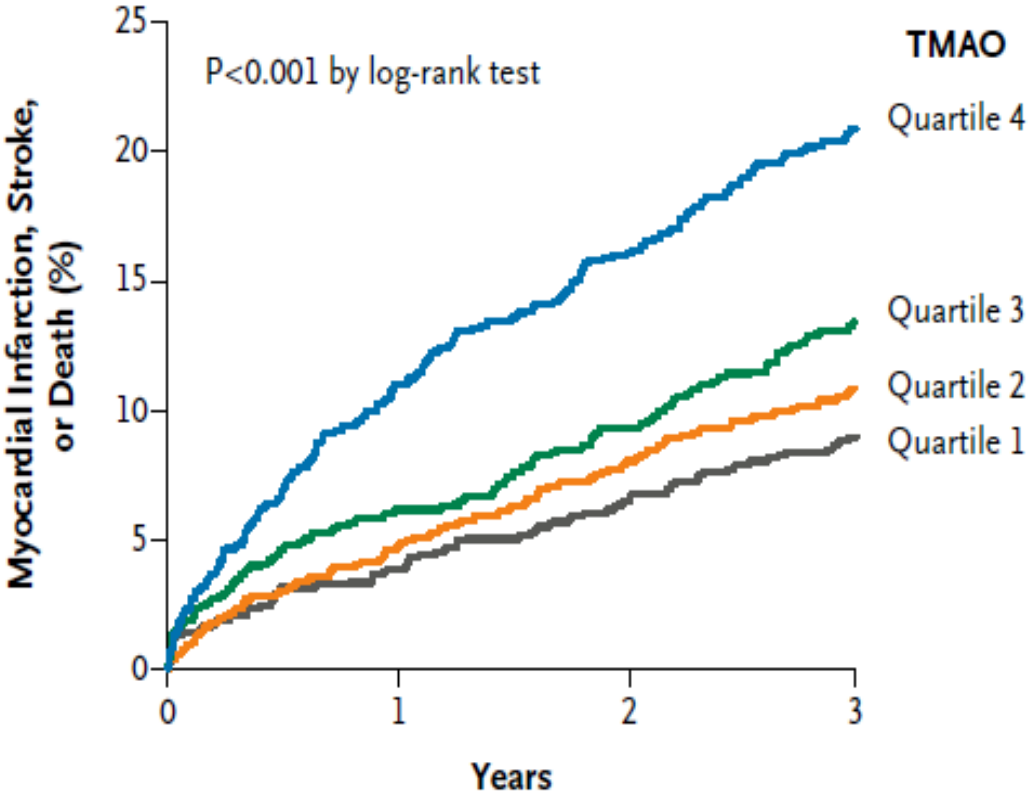
and urine after a week-long treatment with the antibiotics (visit 2)








Antibiotics
(gut flora suppression)
Visit 1
Visit 2
Reacquisition of gut flora
Visit 3
A TMAO
Visit 1
Visit 2
Visit 3
Relative Intensity (%)
100
50
0
0
5
10
Minutes



No. at Risk				
Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

Figure 2. Kaplan–Meier Estimates of Major Adverse Cardiovascular Events, According to the Quartile of TMAO Level.

Neurogastroenterology & Motility

Neurogastroenterol Motil (2014) **26,** 1155–1162 doi: 10.1111/nmo.12378

Correlation between the human fecal microbiota and depression

A. NASERIBAFROUEI,* K. HESTAD,†,‡ E. AVERSHINA,§ M. SEKELJA,§ A. LINLØKKEN,* R. WILSON* & K. RUDI*,§

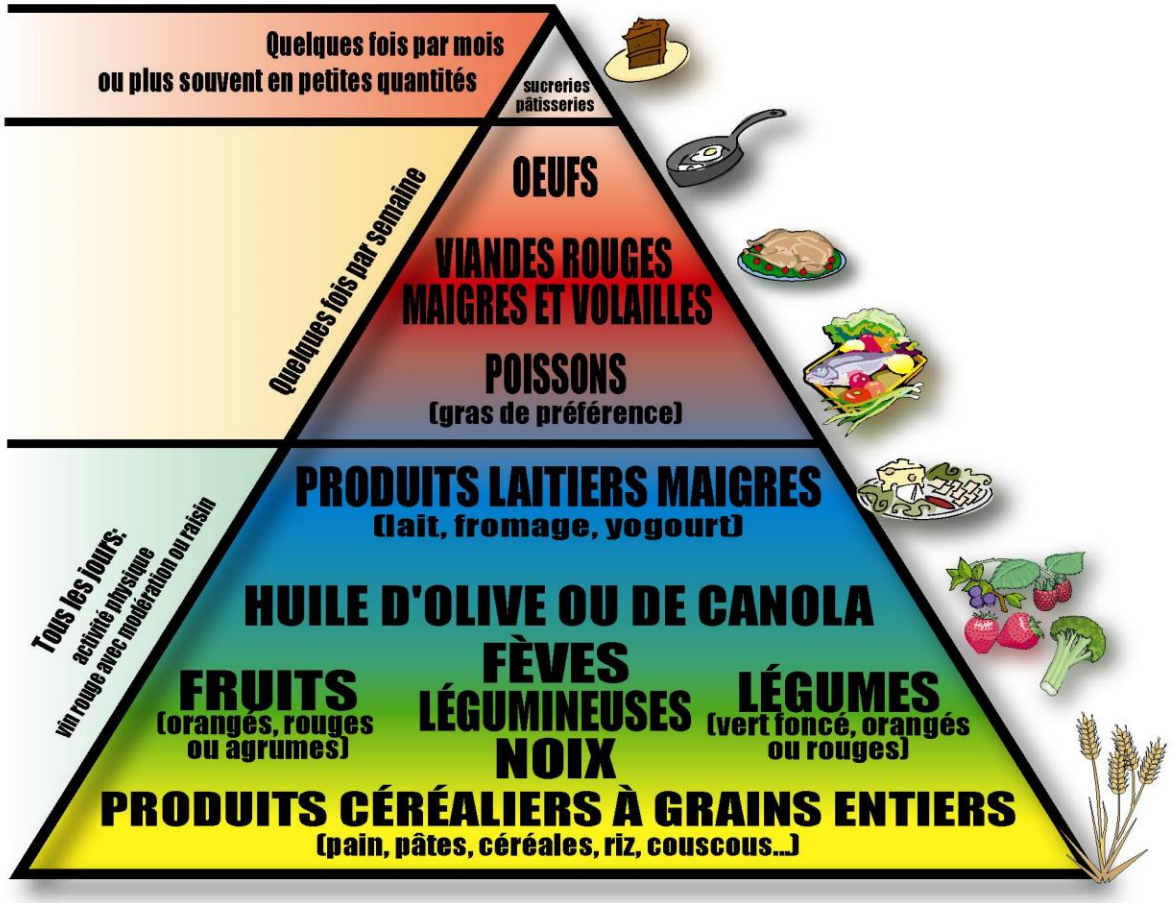
*Faculty of Education and Science, Hedmark University College, Hamar, Norway
†Division of Mental Health, Innlandet Hospital Trust, Hamar, Norway
‡Department of Psychology, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
§Department of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Ås, Norway

Key Messages

- We found a significant correlation between the gut microbiota and depression in humans. The correlations, however, were in opposite directions for closely related Operational Taxonomic Units (OTU's).
- The aim of our work was to investigate the correlation between the human fecal microbiota and depression.
- 16S rRNA gene Illumina deep sequencing from 37 depressed and 18 non-depressed individuals was conducted. The deep sequencing data were analyzed using an in-house generated computer program, enabling the resolution of closely related OTU's.
- The order *Bacteroidales* was overrepresented ($p = 0.05$), while the family *Lachnospiraceae* was underrepresented ($p = 0.02$) with respect to OTU's associated with depression.

ÉPIC

Alimentation Méditerranéenne Modifiée



Microbes et fibres

NATURE COMMUNICATIONS | ARTICLE OPEN

The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism

Gary Frost, Michelle L. Sleeth, Meliz Sahuri-Arisoylu, Blanca Lizarbe, Sebastian Cerdan, Leigh Brody, Jelena Anastasovska, Samar Ghourab, Mohammed Hankir, Shuai Zhang, David Carling, Jonathan R. Swann, Glenn Gibson, Alexander Viardot, Douglas Morrison, E Louise Thomas & Jimmy D. Bell

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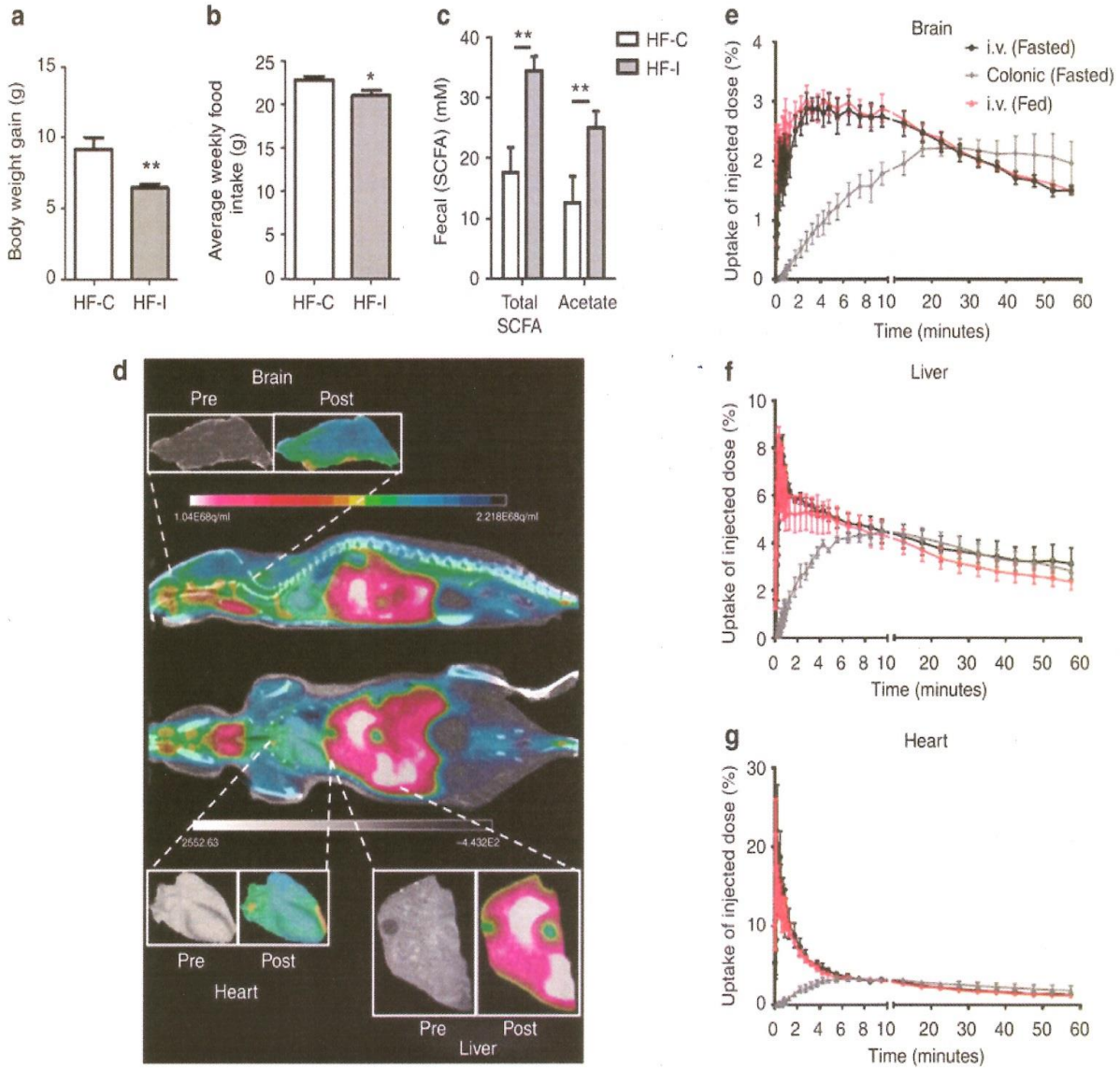
a
Body weight gain (g)
15
10
5
0
**
HF-C
HF-I
b
Average weekly food intake (g)
25
20
15
10
5
0
*
HF-C
HF-I
c
Fecal (SCFA) (mM)
40
30
20
10
0
**
**
HF-C
HF-I
Total SCFA
Acetate
d
Brain
Pre
Post
1.04E68q/ml
2.218E68q/ml
2552.63
4.432E2
Pre
Post
Heart
Pre
Post
Liver
e
Brain
i.v. (Fasted)
Colonic (Fasted)
i.v. (Fed)
Uptake of injected dose (%)
4
3
2
1
0
0 2 4 6 8 10 20 30 40 50 60
Time (minutes)
f
Liver
Uptake of injected dose (%)
10
8
6
4
2
0
0 2 4 6 8 10 20 30 40 50 60
Time (minutes)
g
Heart
Uptake of injected dose (%)
30
20
10
0
0 2 4 6 8 10 20 30 40 50 60
Time (minutes)