Microbiote et risque cardiovasculaire et métabolique

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CHU Toulouse
Fédération de Cardiologie
Service d’hypertension artérielle
INSERM U1048: facteurs de risque intestinaux

Conflits d’intérêt

- Consultant de la société Pileje
- Consultant et détenteur d’action de la société VAIOMER, société spécialisée dans l’étude du microbiote tissulaire.

nature

ARTICLES

An obesity-associated gut microbiome with increased capacity for energy harvest

Peter J. Turnbaugh[1], Ruth E. Ley[1], Michael A. Mahowald[1], Vincent Magrini[2], Elaine R. Mardis[1,2] & Jeffrey I. Gordon[1]

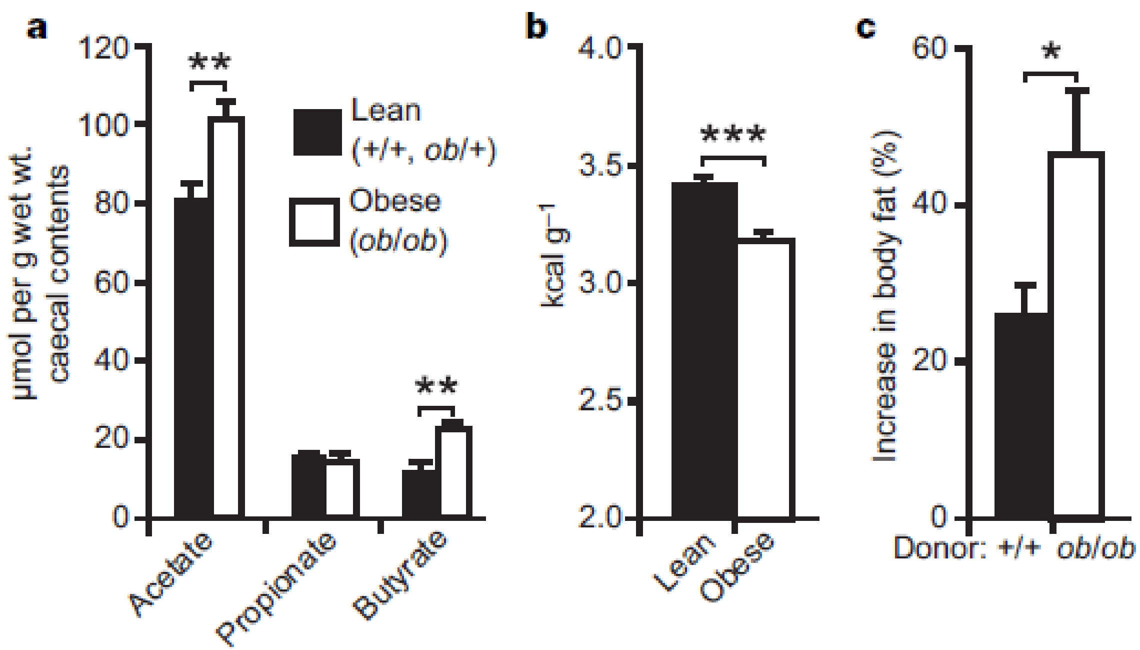


Figure 3 | Biochemical analysis and microbiota transplantation

Gordon et al Nature 21 décembre 2006

Parmi les mécanismes impliqués: la translocation bactérienne

Translocation de métabolites bactériens

TMAO

Endotoxine

ADN bactérien/ bactéries

,,,,,

Trimethylamine-*N*-Oxide : un lien de causalité avec l'athérome

Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease

Zeneng Wang[1,2], Elizabeth Klipfell[1,2], Brian J. Bennett[3], Robert Koeth[1], Bruce S. Levison[1,2], Brandon DuGar[1], Ariel E. Feldstein[1,2], Earl B. Britt[1,2], Xiaoming Fu[1,2], Yoon-Mi Chung[1,2], Yuping Wu[4], Phil Schauer[5], Jonathan D. Smith[1,6], Hooman Allayee[7], W. H. Wilson Tang[1,2,6], Joseph A. DiDonato[1,2], Aldons J. Lusis[3] & Stanley L. Hazen[1,2,6]

RESEARCH ARTICLE

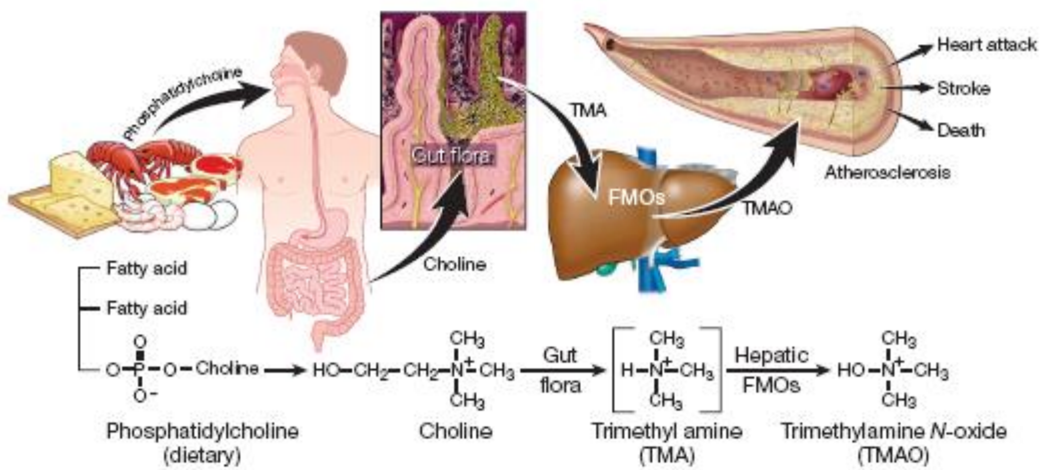
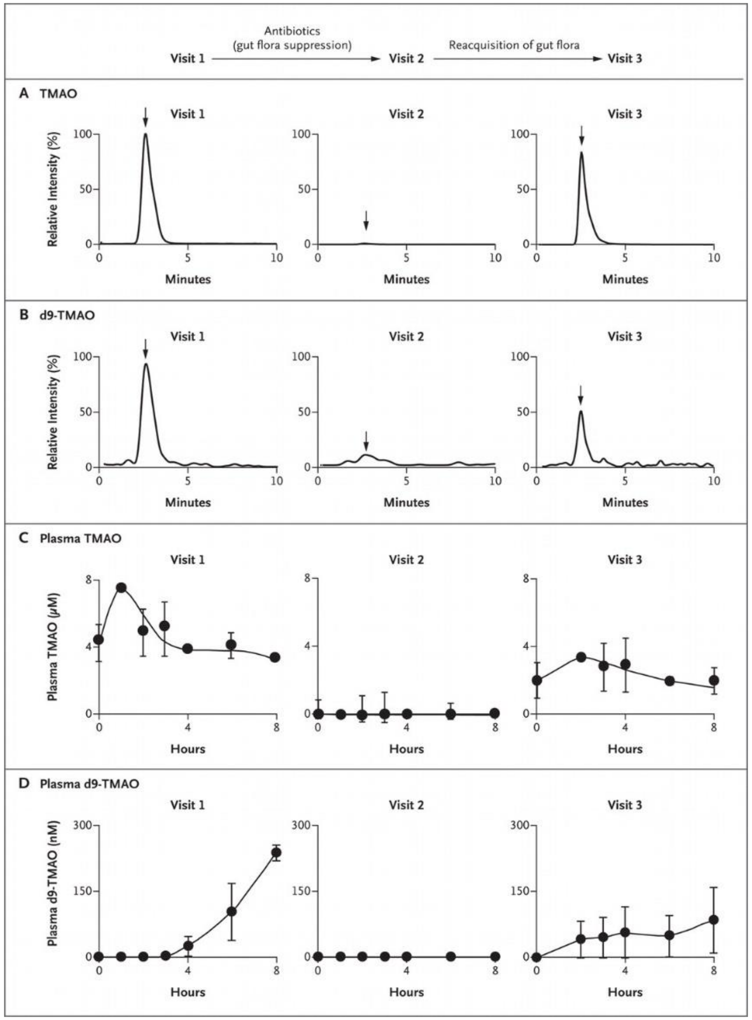


Figure 6 | Gut-flora-dependent metabolism of dietary PC and atherosclerosis. Schematic summary illustrating newly discovered pathway for gut-flora-mediated generation of pro-atherosclerotic metabolite from dietary PC.

Wang et al Nature. 2011 Apr 7;472(7341):57-63

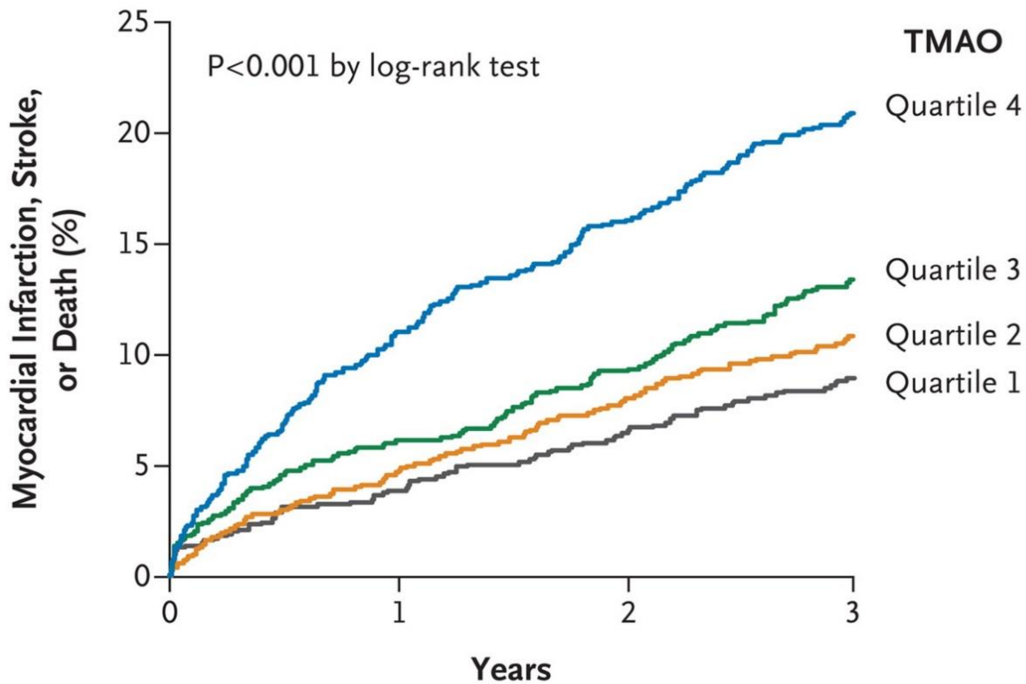
Argument en faveur d'une origine bactérienne du TMAO chez l'homme

Effects of a Phosphatidylcholine Challenge and Administration of Antibiotics on Mean Levels of Trimethylamine-*N*-Oxide (TMAO) and Its d9 Isotopologue (d9-TMAO).



Tang W et al. N Engl J Med 2013;368:1575-1584.

Concentration plasmatique de TMAO et risque cardiovasculaire

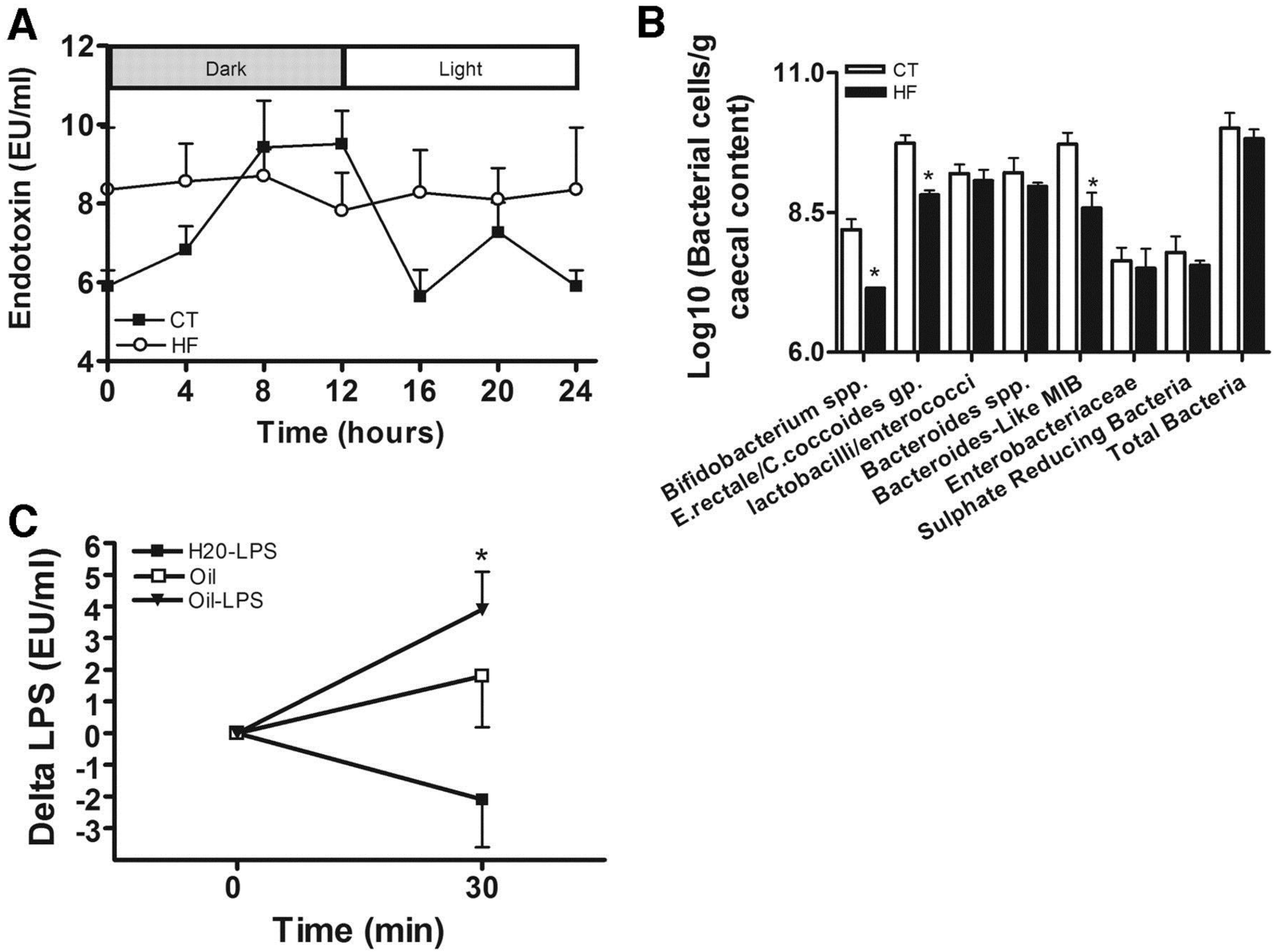


No. at Risk

Quartile 1	1001	933	869	827
Quartile 2	998	940	884	843
Quartile 3	1003	938	888	835
Quartile 4	1005	913	849	791

Tang W et al. N Engl J Med 2013;368:1575-1584.

Endotoxinémie: un lien de causalité avec le diabète



Cani P D, Amar J et al. Diabetes 2007;56:1761-1772

Un pont entre les habitudes alimentaires et les pathologies cardio-métaboliques

Energy intake is associated with endotoxemia in apparently healthy men[1–4]

Jacques Amar, Rémy Burcelin, Jean Bernard Ruidavets, Patrice D Cani, Josette Fauvel, Marie Christine Alessi, Bernard Chamontin, and Jean Ferriéres

TABLE 2
Relations between energy and fat intakes and endotoxemia (linear regression of energy or fat on endotoxemia)

	Total energy[1]			Energy without alcohol[1]			Fat[2]			Fat[3]		
	β	SE	P	β	SE	P	β	SE	P	β	SE	P
Endotoxin concentration												
<9 U/L	0			0			0			0		
9–39 U/L	62.9	51.0	0.22	57.9	46.9	0.22	1.2	3.1	0.71	0.9	1.8	0.61
>39 U/L	132.2	62.7	0.04	121.8	57.7	0.04	4.6	3.8	0.23	2.5	2.1	0.26
P for trend	0.03	—	—	0.03	—	—	0.25	—	—	0.25	—	—

[1] Adjusted for age, physical activity, BMI, and residuals from linear regression of energy on protein, carbohydrate, fat, and alcohol.
[2] Linear regression of fat-adjusted energy on endotoxemia.
[3] Adjusted for age, physical activity, BMI, and residuals from linear regression of energy on protein, carbohydrate, and alcohol.

Am J Clin Nutr 2008;87:1219–23.

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PII S0735-1097(99)00448-9

Atherosclerosis

Association of Endotoxemia With Carotid Atherosclerosis and Cardiovascular Disease

Prospective Results from the Bruneck Study

Christian J. Wiedermann, MD,* Stefan Kiechl, MD,† Stefan Dunzendorfer, MD,*
Peter Schratzberger, MD,* Georg Egger, MD,‡ Friedrich Oberhollenzer, MD,‡ Johann Willeit, MD†
Innsbruck, Austria, and Bruneck, Italy

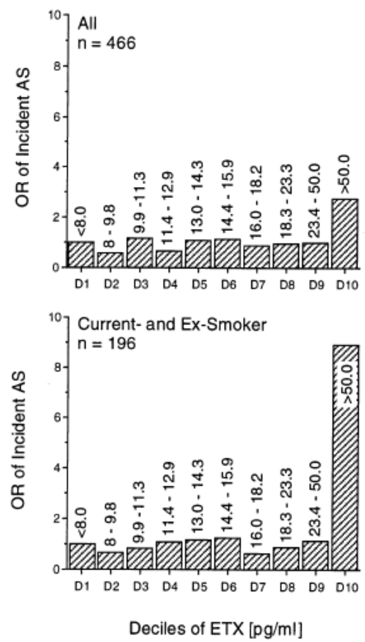
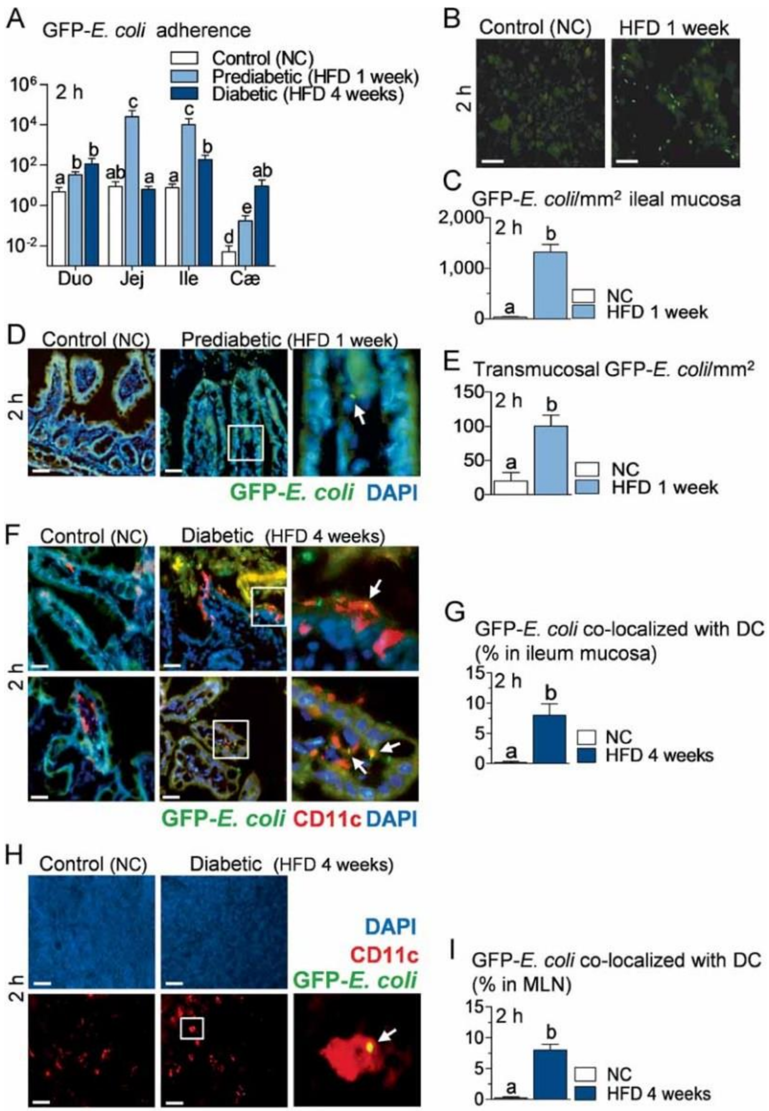


Figure 2. Binary-type association between endotoxin plasma level and atherosclerosis risk. OR = odds ratio; AS = atherosclerosis.

Wiedermann et al. JACC 1999

ADN bactérien/ bactéries

Intestinal mucosal adherence and translocation of commensal bacteria at the early onset of type 2 diabetes: molecular mechanisms and probiotic treatment.



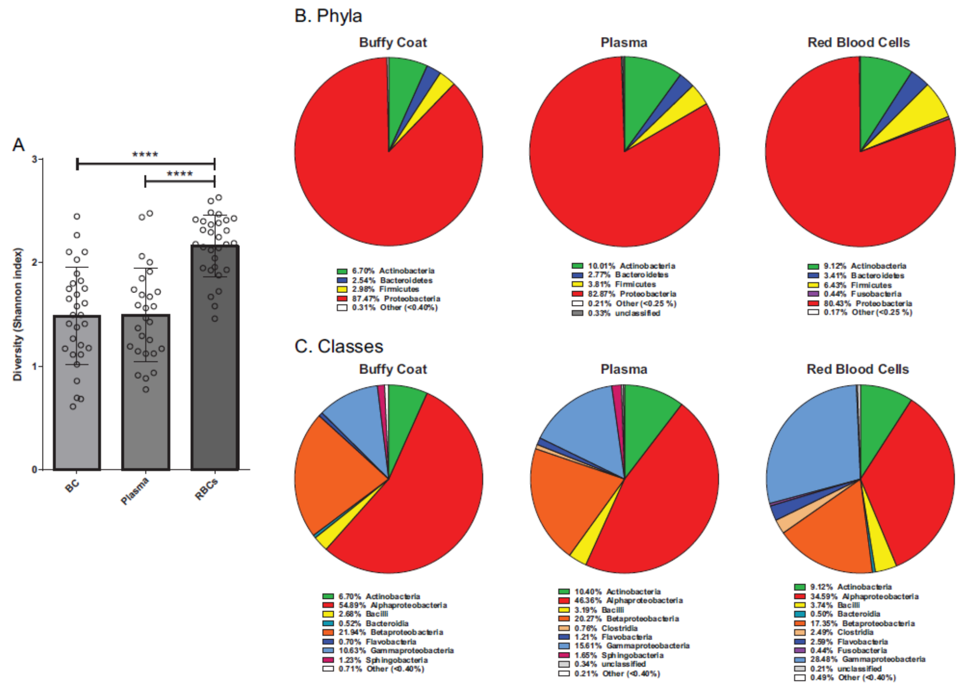
Amar et al EMBO Mol med sept 2011

Photographie du microbiote sanguin du sujet « sain »

BLOOD COMPONENTS

Comprehensive description of blood microbiome from healthy donors assessed by 16S targeted metagenomic sequencing

Sandrine Païssé,[1] Carine Valle,[1]* Florence Servant,[1] Michael Courtney,[1] Rémy Burcelin,[1,2] Jacques Amar,[1,3]* and Benjamin Lelouvier[1]**

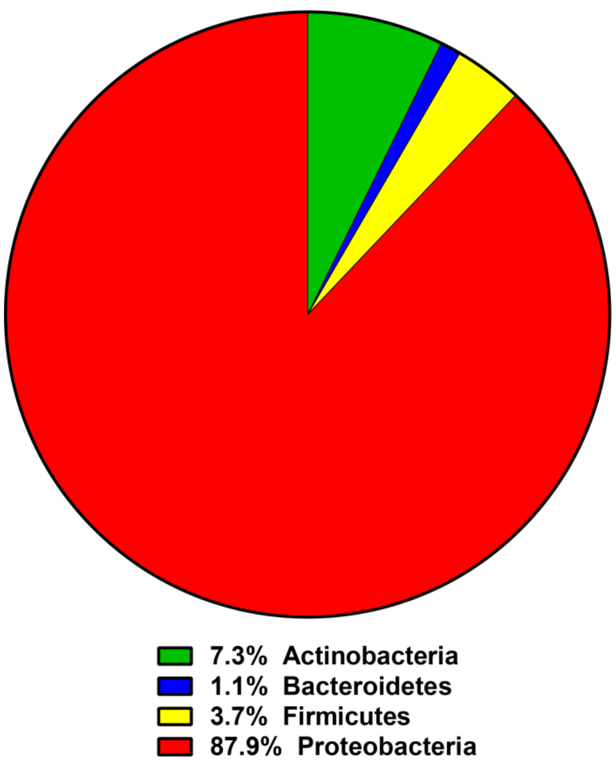


Paisse et al. Transfusion 2016

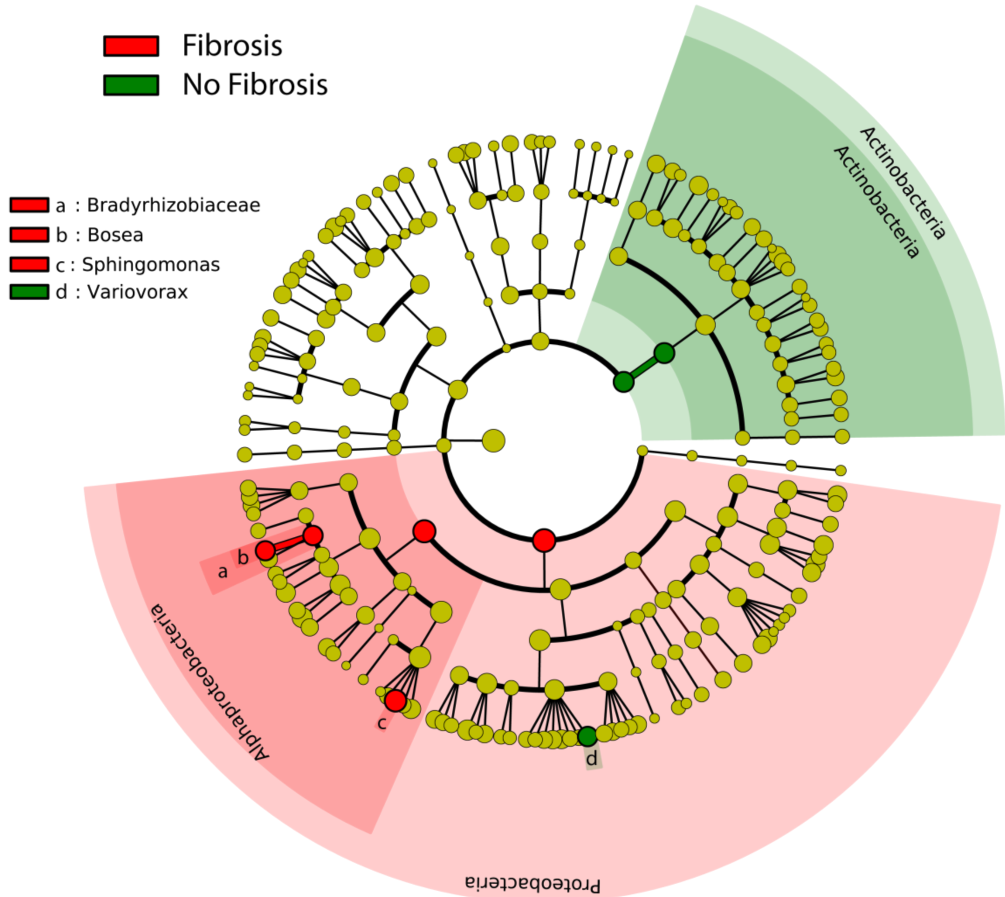
Profil d'ADN bactérien sanguin associé à la fibrose hépatique métabolique

Blood bacterial taxa assessed by 16S metagenomic sequencing in buffy coats of control individuals or patients with liver fibrosis.

a- Blood phyla - all patients



b- LEfSe Dendrogram



Amar et al **Hepatology 2016,**

Mitra et al. Microbiome (2015) 3:38
DOI 10.1186/s40168-015-0100-y

Microbiome

RESEARCH Open Access

Métagénome de la plaque d'athérome

In silico analyses of metagenomes from human atherosclerotic plaque samples

Suparna Mitra[1,2,3*], Daniela I. Drautz-Moses[1], Morten Alhede[5], Myat T. Maw[1], Yang Liu[1], Rikky W. Purbojati[1], Zhei H. Yap[1], Kavita K. Kushwaha[1], Alexandra G. Gheorghe[4], Thomas Bjarnsholt[5,7], Gorm M. Hansen[5,8], Henrik H. Sillesen[4], Hans P. Hougen[4], Peter R. Hansen[8], Liang Yang[1], Tim Tolker-Nielsen[5], Stephan C. Schuster[1] and Michael Givskov[1,5*]

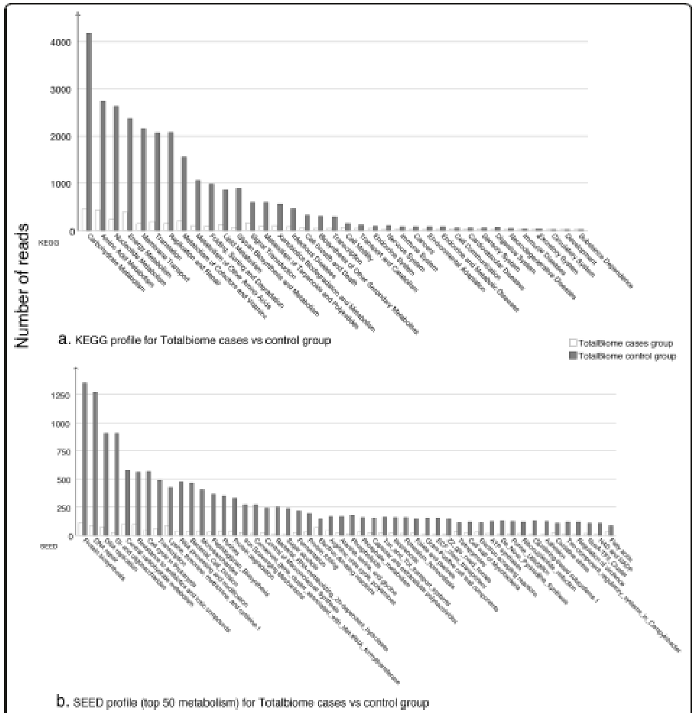
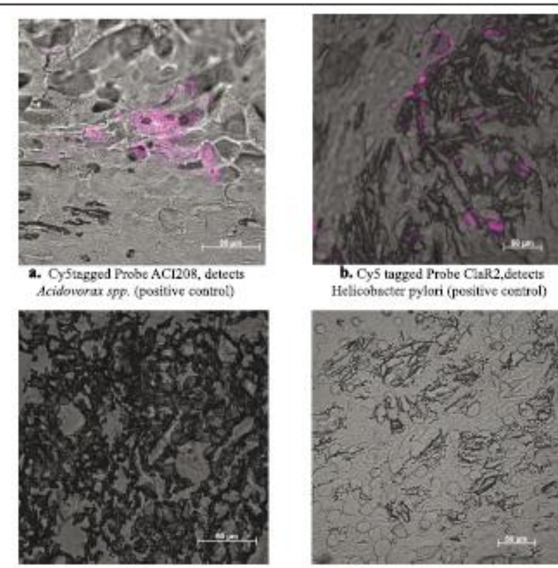


Fig. 6 Functional comparison of total biome. Differences between total biome for unstable atherosclerotic plaque samples (*white*) and stable plaque samples (*blue*) are displayed with comparative bar charts. **a** depicts the difference of KEGG orthologies (level 2) and **b** provides comparison of the two groups with the top 50 SEED level 2 subsystems



a. Cy5tagged Probe ACI208, detects *Acidovorax spp.* (positive control)

b. Cy5 tagged Probe ClaR2,detects Helicobacter pylori (positive control)

c. Cy5 tagged ProbeTM7305,for subdivision 1of candidate division TM7(negative control)

d. Cy5 tagged Probe PAR651, for detection of *Paracoccus spp.*(negative control)

Fig. 7 FISH images of *Acidovorax* spp. and *H. pylori* in atherosclerotic plaque samples. Representative results of plaque samples after applying the *Acidovorax* spp.-specific probe (**a**), *H. pylori*-specific probe (**b**), as well as two negative control probes, i.e., *Candidate division TM7* (**c**), and *Paracoccus* spp. (**d**), on atherosclerotic plaque material from several different patients. We observed morphogically distinct clusters of *Acidovorax* spp. and *H. pylori* cells surrounded by atherosclerotic tissue material

Mitra et al Microbiome 2015,

Blood Microbiota Dysbiosis and Cardiac Events

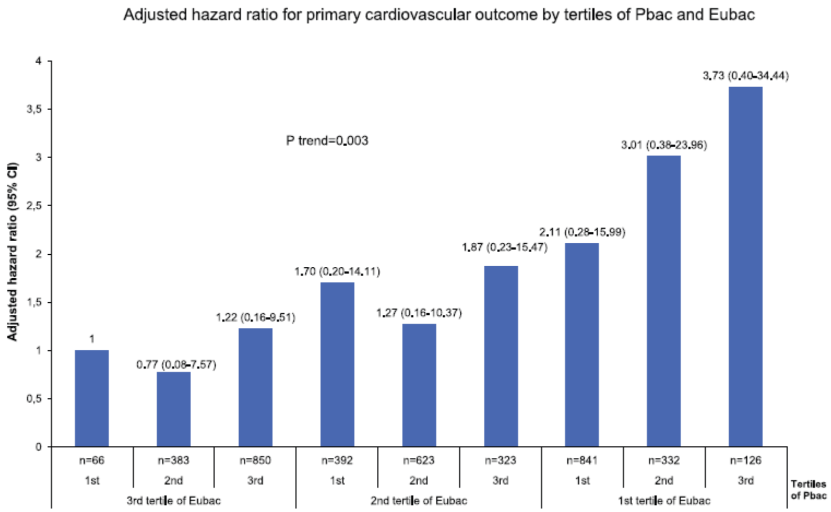


Figure 2. Adjusted Hazard ratio of having primary cardiovascular outcome by tertiles of Eubacteria (Eubac) and Proteobacteria (Pbac).
doi:10.1371/journal.pone.0054461.g002

Diabetologia (2011) 54:3055–3061
DOI 10.1007/s00125-011-2329-8

ARTICLE

Involvement of tissue bacteria in the onset of diabetes in humans: evidence for a concept

3060

Table 4 Adjusted ORs (95% CI) of incident diabetes for 1 SD of log (16S rDNA gene concentration) in the overall population and in various strata

Variable	Incident diabetes (*n*)	OR[a]	95% CI	*p* value
Overall	131	1.35	1.11, 1.64	0.002

Amar et al Diabetologia 2011; PlosOne 2013

Quelles applications en pathologie cardiovasculaire en 2017?

1. modifier la flore par antibiothérapie

2. modifier la flore par une stratégie pré ou probiotique

3. modifier le passage intestinal des bactéries

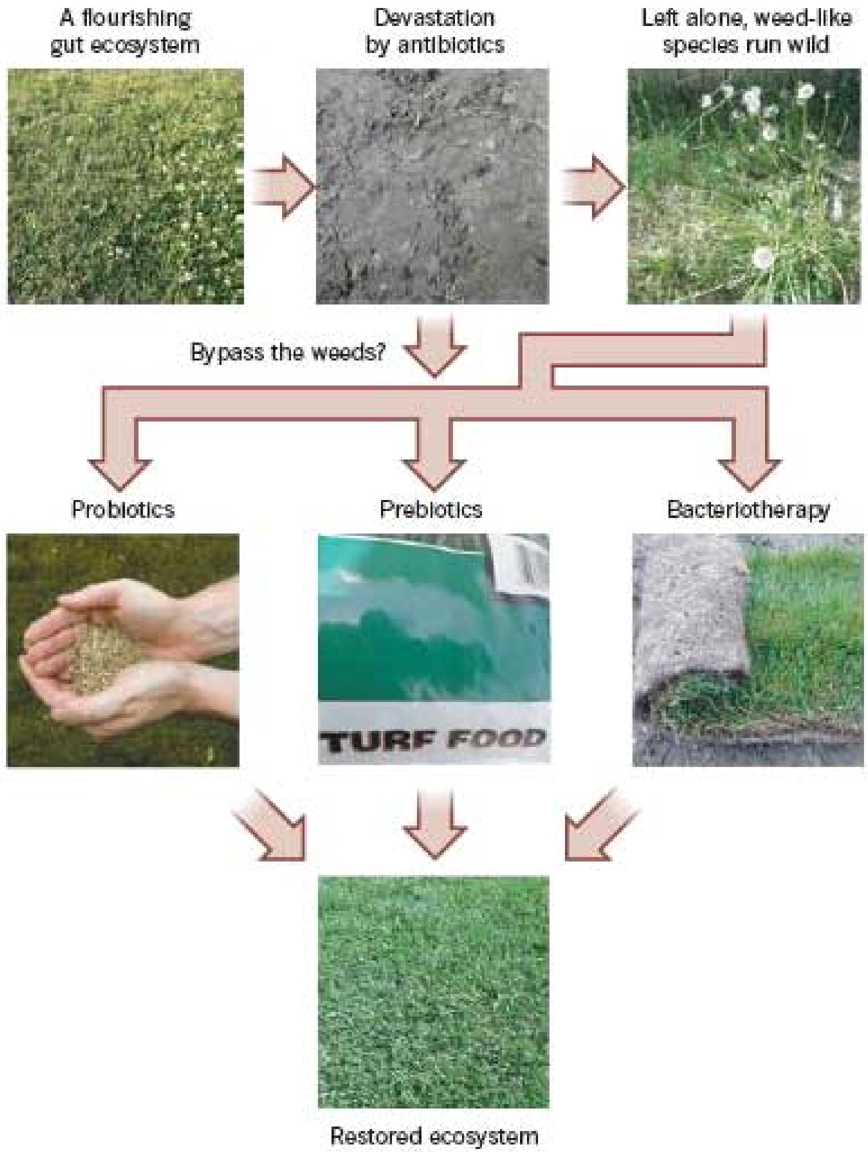
Cibler un écosystème et pas un pathogène

REVIEW

doi:10.1038/nature11550

Diversity, stability and resilience of the human gut microbiota

Catherine A. Lozupone[1], Jesse I. Stombaugh[1], Jeffrey I. Gordon[2], Janet K. Jansson[3,4] & Rob Knight[1,5,6]

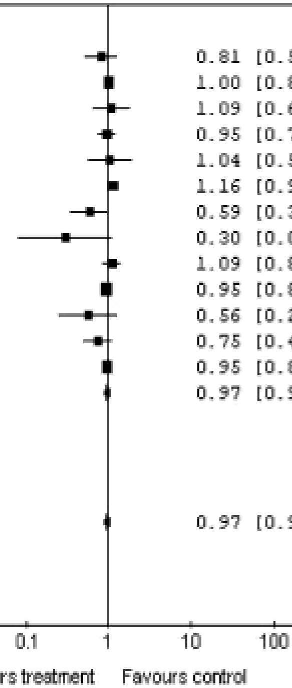


Les raisons de l'échec d'une stratégie antibiotique en pathologie cardiovasculaire

Study	Treatment n/N	Control n/N	RR (random) 95% CI	Year
ACADEMIC	28/150	35/152	0.81 [0.52, 1.26]	2000
ACES	446/2004	449/2008	1.00 [0.89, 1.12]	2004
ANTIBIO	28/433	26/439	1.09 [0.65, 1.83]	2004
AZACS	100/716	106/723	0.95 [0.74, 1.23]	2003
Berg et al	20/238	19/235	1.04 [0.57, 1.90]	2005
CLARICOR	249/2172	218/2200	1.16 [0.97, 1.37]	2006
CLARIFY	16/74	27/74	0.59 [0.35, 1.00]	2002
Gupta et al	3/40	5/20	0.30 [0.08, 1.13]	1997
ISAR-3	96/509	90/518	1.09 [0.84, 1.41]	2001
PROVE IT	493/2076	524/2086	0.95 [0.85, 1.05]	2000
ROXIS	8/102	14/100	0.56 [0.25, 1.28]	1999
STAMINA	28/111	36/107	0.75 [0.49, 1.14]	2002
WIZARD	551/3866	579/3856	0.95 [0.85, 1.06]	2001
Subtotal (95% CI)	12491	12518	0.97 [0.90, 1.04]	
Total (95% CI)	12491	12518	0.97 [0.90, 1.04]	

Subtotal: Total events: 2066 (Treatment), 2128 (Control)
Test for heterogeneity: $\chi^2 = 15.77$, df = 12 (P = 0.20), $I^2 = 23.9\%$
Test for overall effect: Z = 0.88 (P = 0.38)

Total: Total events: 2066 (Treatment), 2128 (Control)
Test for heterogeneity: $\chi^2 = 15.77$, df = 12 (P = 0.20), $I^2 = 23.9\%$
Test for overall effect: Z = 0.88 (P = 0.38)



Il ne s'agit pas d'éradiquer un pathogène mais de modifier l'équilibre d'une flore?

Z Song, P Brassard, JM Brophy. A meta-analysis of antibiotic use for the secondary prevention of cardiovascular diseases. Can J Cardiol 2008;24(5):391-395.

1. modifier la flore par antibiothérapie

2. modifier la flore par une stratégie pré ou probiotique

3. modifier le passage intestinal des bactéries

High-Fiber Diet and Acetate Supplementation Change the Gut Microbiota and Prevent the Development of Hypertension and Heart Failure in Hypertensive Mice

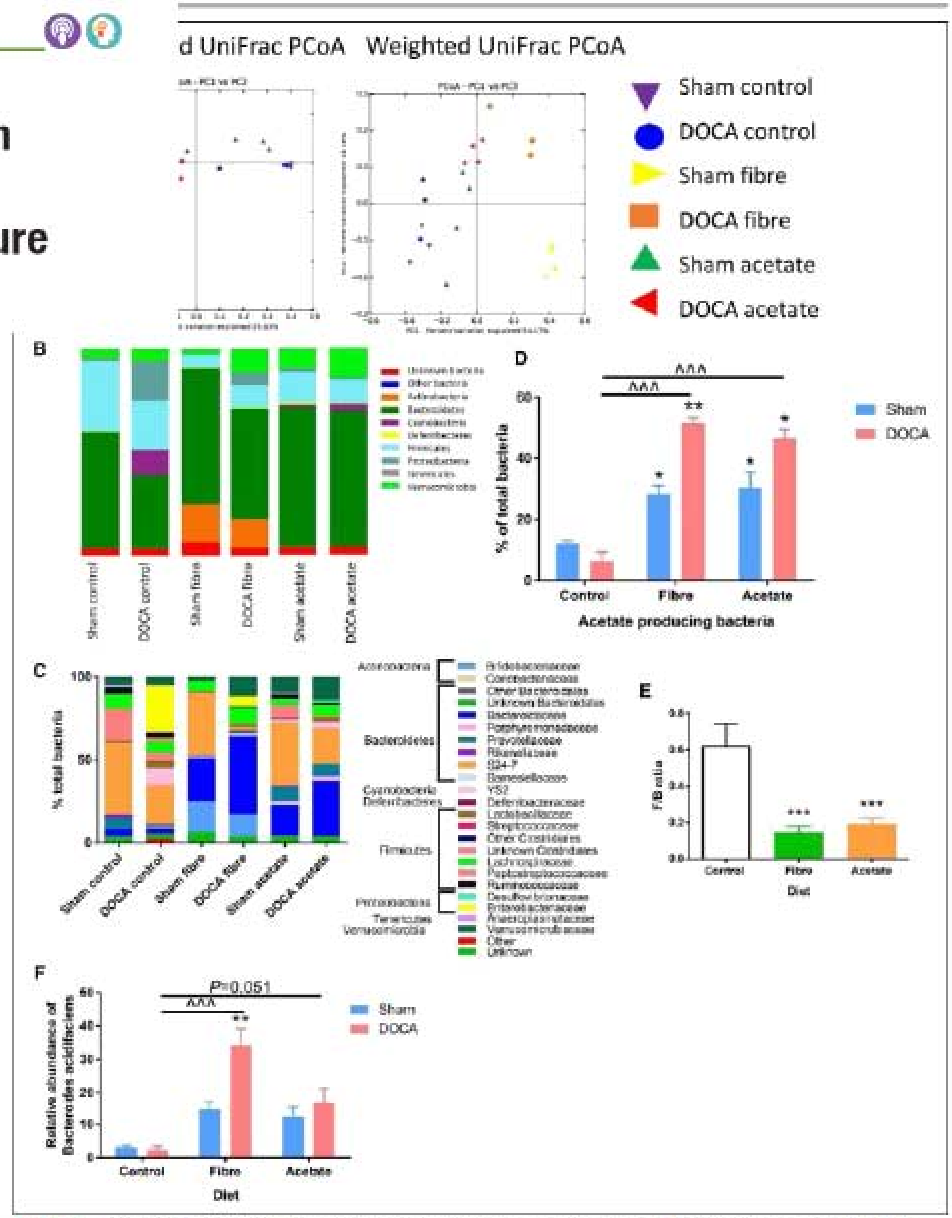


Figure 1. The effect of deoxycorticosterone acetate (DOCA)–salt, a diet rich in fiber and acetate supplementation, in the gut microbiome.
A, The composition of the gut microbiota between sham and DOCA mice fed a control or high-fiber diet is significantly different. Shown are unweighted (**left**; P=0.001) and weighted (**right**; P=0.001) UniFrac principal coordinate analyses (PCoA). (*Continued*)

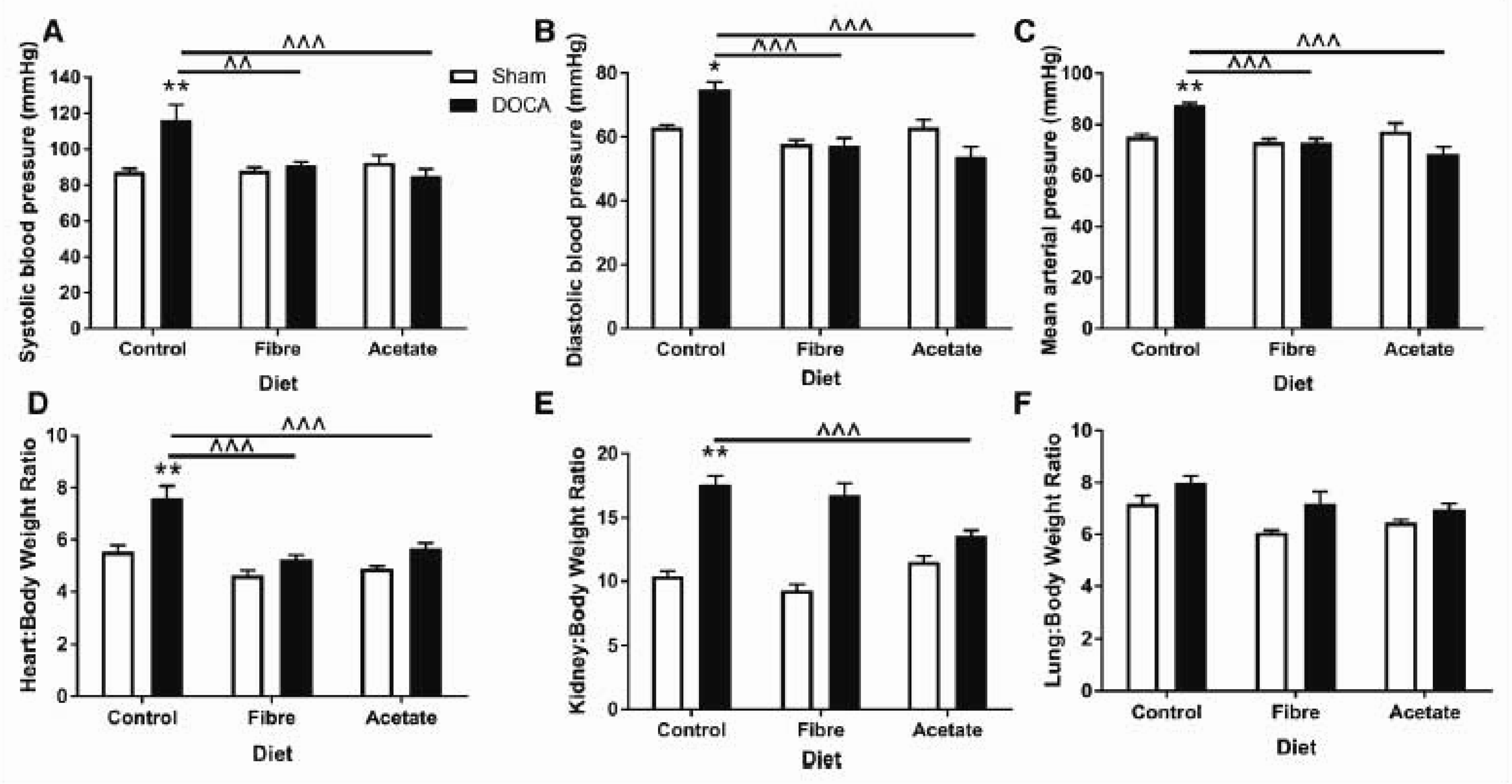


Figure 2. High-fiber diet and acetate modulate blood pressure and heart and kidney weight in deoxycorticosterone acetate (DOCA)–salt model.

Compared with controls, animals exposed to mineralocorticoid excess had a significant increase in (**A**) systolic blood pressure, (**B**) diastolic blood pressure, and (**C**) mean arterial pressure. All were significantly reduced by a high-fiber diet or acetate complementation. **D**, Compared with controls, DOCA-salt mice had significantly larger cardiac weight index, which was reduced by a high-fiber diet or acetate complementation. **E**, Kidney weight (relative to body weight) of DOCA-salt mice was also increased, and acetate significantly reduced it. **F**, There was no difference in lung weight (adjusted by body weight) between groups. Values are mean±SEM. **P*<0.05, ***P*<0.01, ^^^*P*<0.001 vs DOCA-control.

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Fresh Fruit Consumption and Major Cardiovascular Disease in China

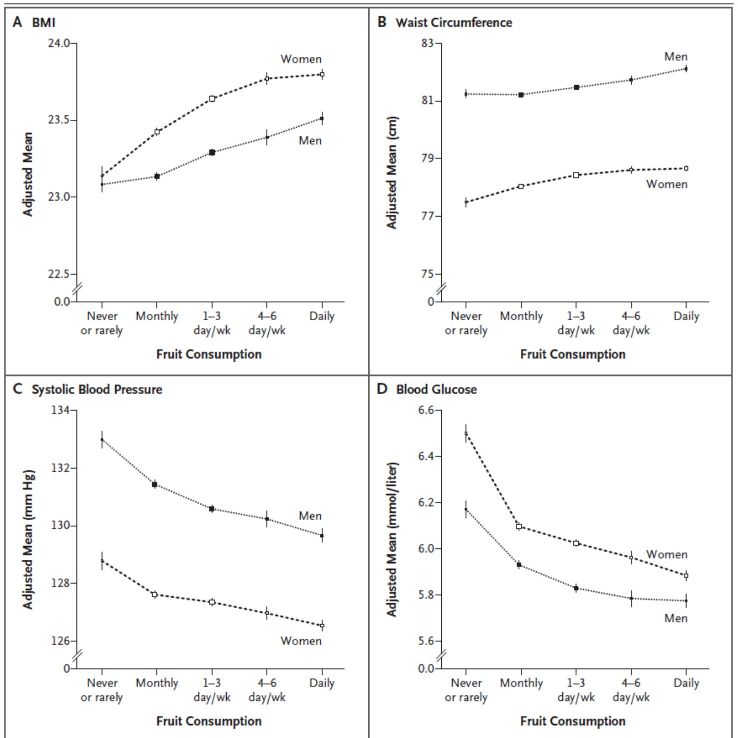


Figure 1. Adjusted Mean Body-Mass Index (BMI), Waist Circumference, Blood Pressure, and Blood Glucose According to the Frequency of Fresh Fruit Consumption.

Mean values for BMI (Panel A) and waist circumference (Panel B) were adjusted for age (10 categories), area of China (10 regions), educational level (4 categories), annual household income (4 categories), smoking status (4 categories, with the category of "Never" subdivided into "Never" and "Occasional"), alcohol intake (4 categories, with the category of "Never" subdivided into "Never" and "Occasional"), physical activity (continuous variable), survey season (4 categories), and consumption of meat (3 categories), dairy products (3 categories), and preserved vegetables (5 categories). Mean values for systolic blood pressure (Panel C) and random blood glucose measurements (Panel D) were adjusted for the listed variables plus BMI and waist circumference. Blood glucose values were missing for 7503 study participants. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. Vertical lines indicate 95% confidence intervals. P<0.001 for trend, for all comparisons.

Un demi million de personnes

The NEW ENGLAND JOURNAL *of* MEDICINE

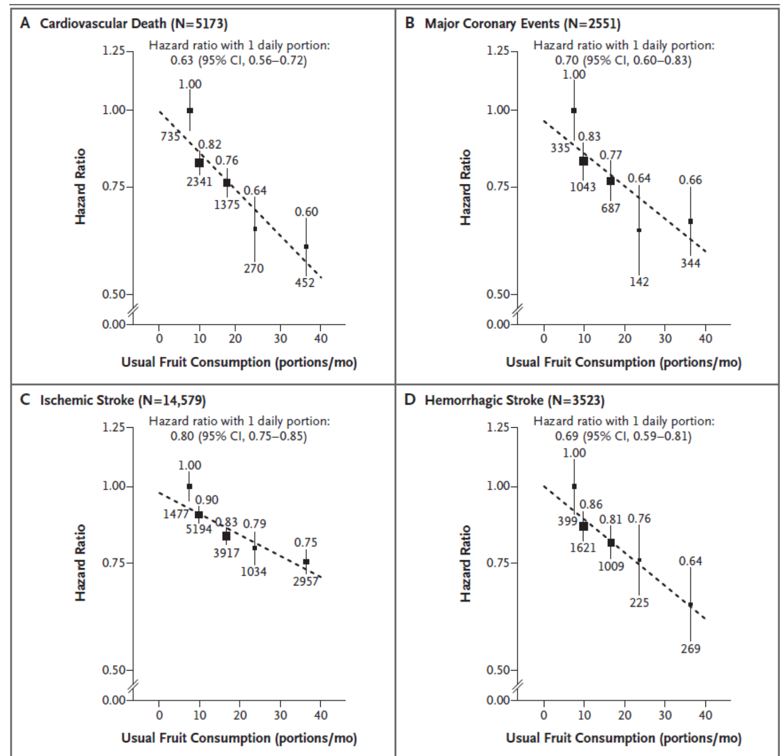


Figure 2. Adjusted Hazard Ratios for Major Cardiovascular Events According to the Level of Fresh Fruit Consumption.

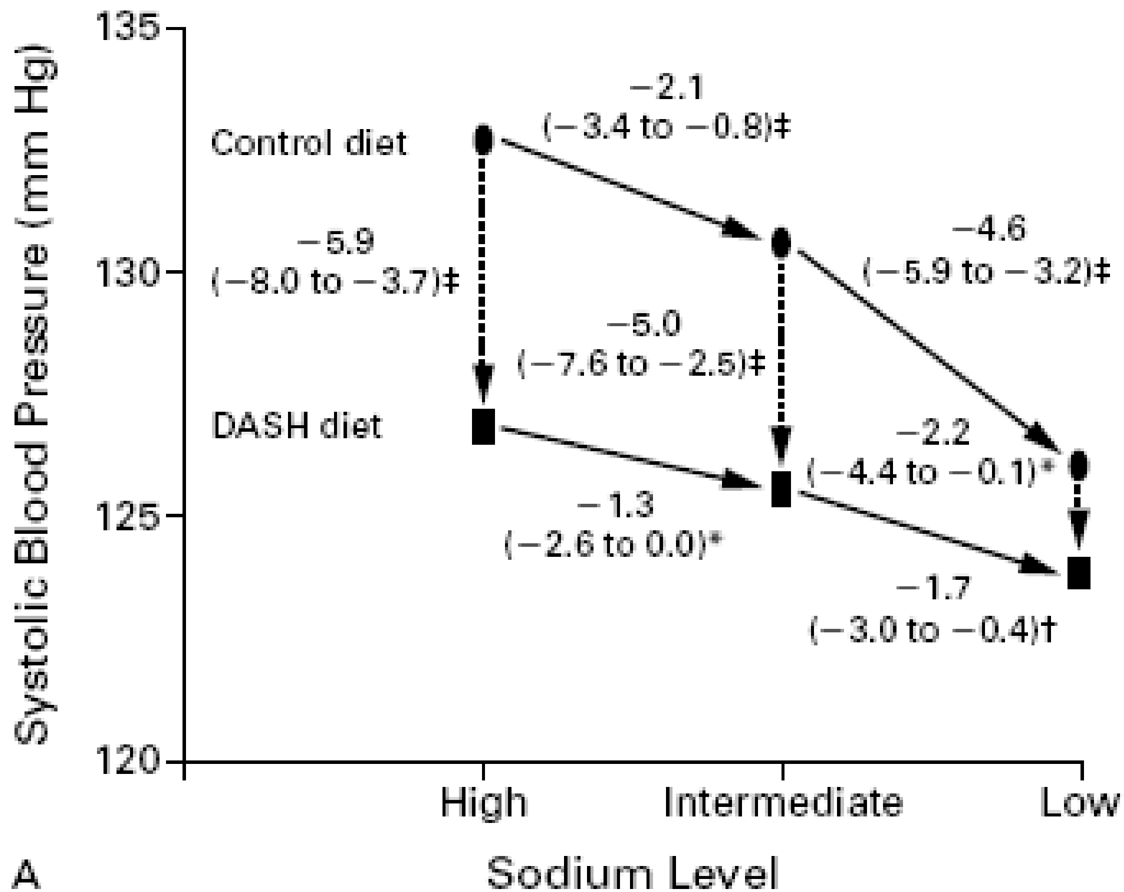
Analyses were adjusted for educational level, income, alcohol intake, smoking status, physical activity, survey season, and consumption of dairy products, meat, and preserved vegetables and were stratified according to age at risk, sex, and region. The black boxes represent hazard ratios, with the size inversely proportional to the variance of the logarithm of the hazard ratio, and the vertical lines represent 95% confidence intervals. The numbers above the vertical lines are point estimates for hazard ratios, and the numbers below the lines are numbers of events.

Du et al N Engl J Med. 2016;374:1332-43.2016

VOLUME 344 JANUARY 4, 2001 NUMBER 1

EFFECTS ON BLOOD PRESSURE OF REDUCED DIETARY SODIUM AND THE DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET

Frank M. Sacks, M.D., Laura P. Svetkey, M.D., William M. Vollmer, Ph.D., Lawrence J. Appel, M.D., George A. Bray, M.D., David Harsha, Ph.D., Eva Obarzanek, Ph.D., Paul R. Conlin, M.D., Edgar R. Miller III, M.D., Ph.D., Denise G. Simons-Morton, M.D., Ph.D., Njeri Karanja, Ph.D., and Pao-Hwa Lin, Ph.D., for the DASH–Sodium Collaborative Research Group



***Sachs et al N Engl J Med**. 2001.*

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 4, 2013 VOL. 368 NO. 14

Participants in the two Mediterranean-diet groups received either extra-virgin olive oil (approximately 1 liter per week) or 30 g of mixed nuts per day (15 g of walnuts, 7.5 g of hazelnuts, and 7.5 g of almonds) at no cost, and those in the control group received small nonfood gifts. **No total calorie restriction was advised, nor was physical activity promoted.**

Étude conduite en pays méditerranéen (Espagne)

Groupe contrôle: Régime méditeranéen + Conseil pour une diminution du contenu en graisses

Régime méditerranéen + Huile d'olive extra vierge (1l par semaine)

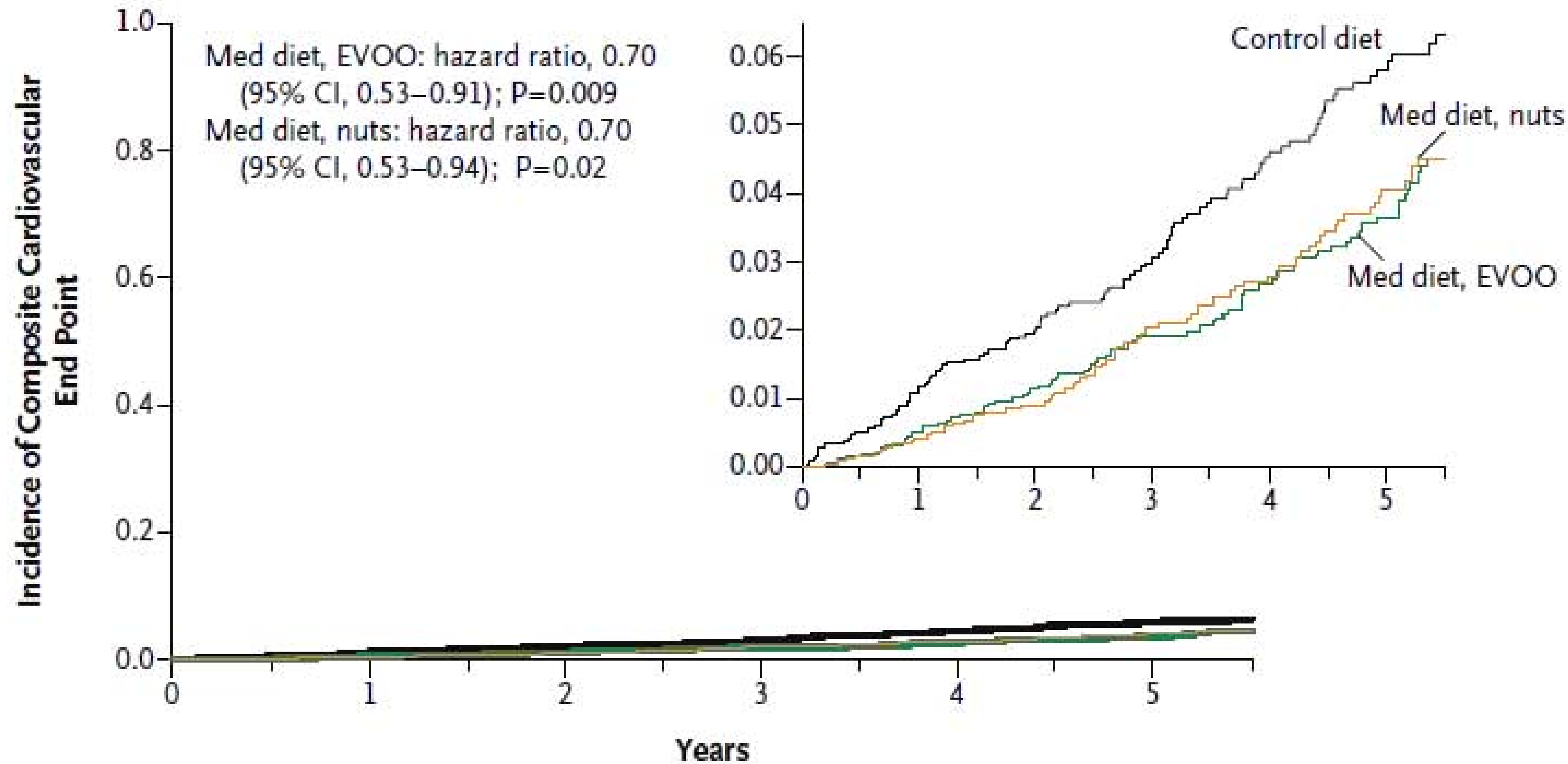
Régime méditerranéen + noisettes + Noix + Amandes (30g/jour)

Estruch et al N Engl J Med. 2013 Apr 4;368(14):1279-90.

The NEW ENGLAND JOURNAL of MEDICINE
APRIL 4, 2013

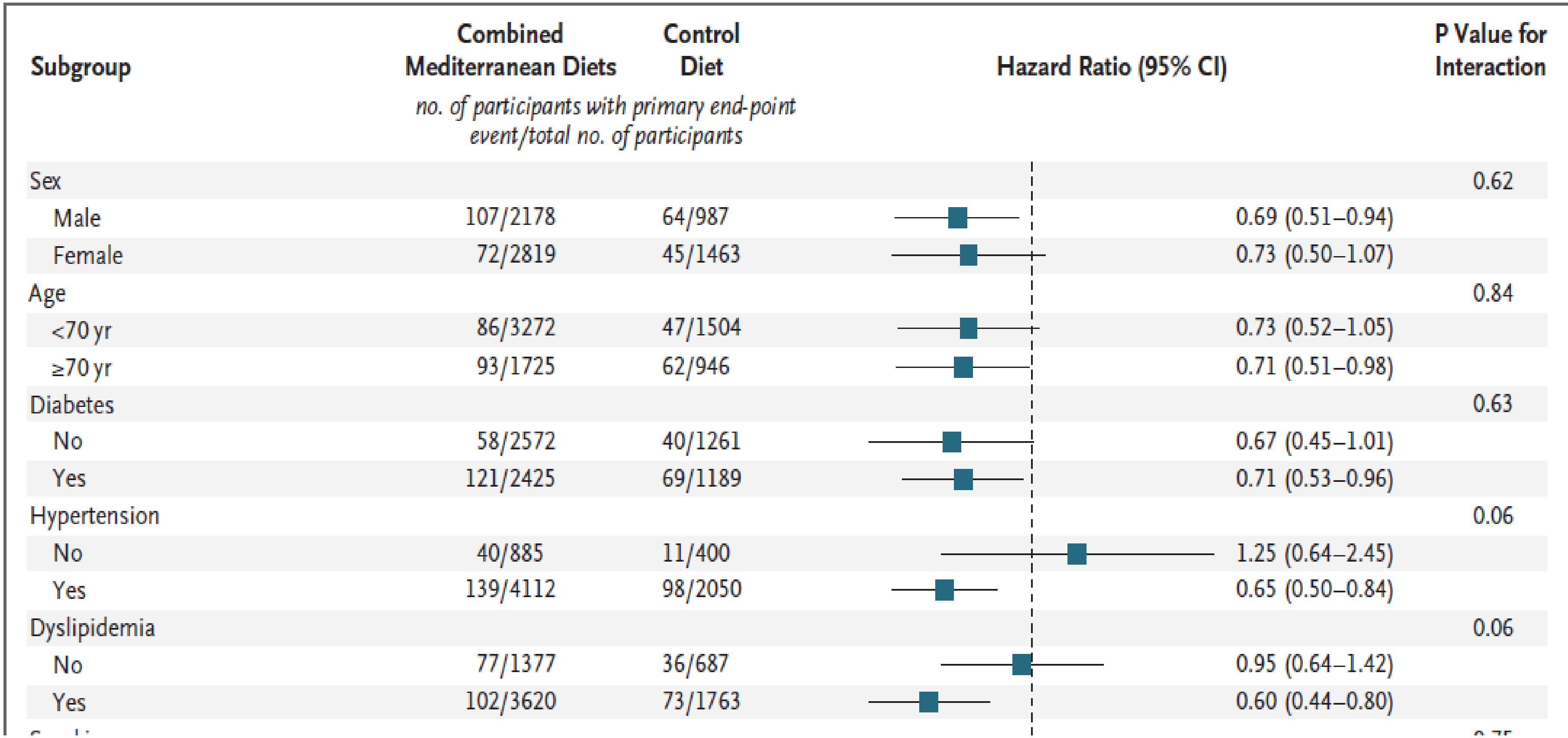
Primary Prevention of Cardiovascular Disease
with a Mediterranean Diet

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)



No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031



Subgroup	Combined Mediterranean Diets	Control Diet	Hazard Ratio (95% CI)	P Value for Interaction
	no. of participants with primary end-point event/total no. of participants			
Sex				0.62
Male	107/2178	64/987	0.69 (0.51–0.94)	
Female	72/2819	45/1463	0.73 (0.50–1.07)	
Age				0.84
<70 yr	86/3272	47/1504	0.73 (0.52–1.05)	
≥70 yr	93/1725	62/946	0.71 (0.51–0.98)	
Diabetes				0.63
No	58/2572	40/1261	0.67 (0.45–1.01)	
Yes	121/2425	69/1189	0.71 (0.53–0.96)	
Hypertension				0.06
No	40/885	11/400	1.25 (0.64–2.45)	
Yes	139/4112	98/2050	0.65 (0.50–0.84)	
Dyslipidemia				0.06
No	77/1377	36/687	0.95 (0.64–1.42)	
Yes	102/3620	73/1763	0.60 (0.44–0.80)	

Un bénéfice particulier pour les hypertendus et les dyslipidémiques

Conclusion et Synthèse pour la pratique

- **Au sein de nos tissus, des métabolites et de l'ADN bactérien agissent sur le système cardio-métabolique.**

- **Un régime de type méditerranéen riche en fibre :**
  - **a un impact sur le pronostic cardiovasculaire, la pression artérielle et le remodelage cardiaque**
  - **Cet effet est expliqué au moins partiellement par une modification du microbiote.**
  - Il doit être préconisé à nos patients à haut risque cardiovasculaire y compris en prévention secondaire