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Strain-level Dissection of the Gut Microbiome Contribution to Human Metabolic Diseases

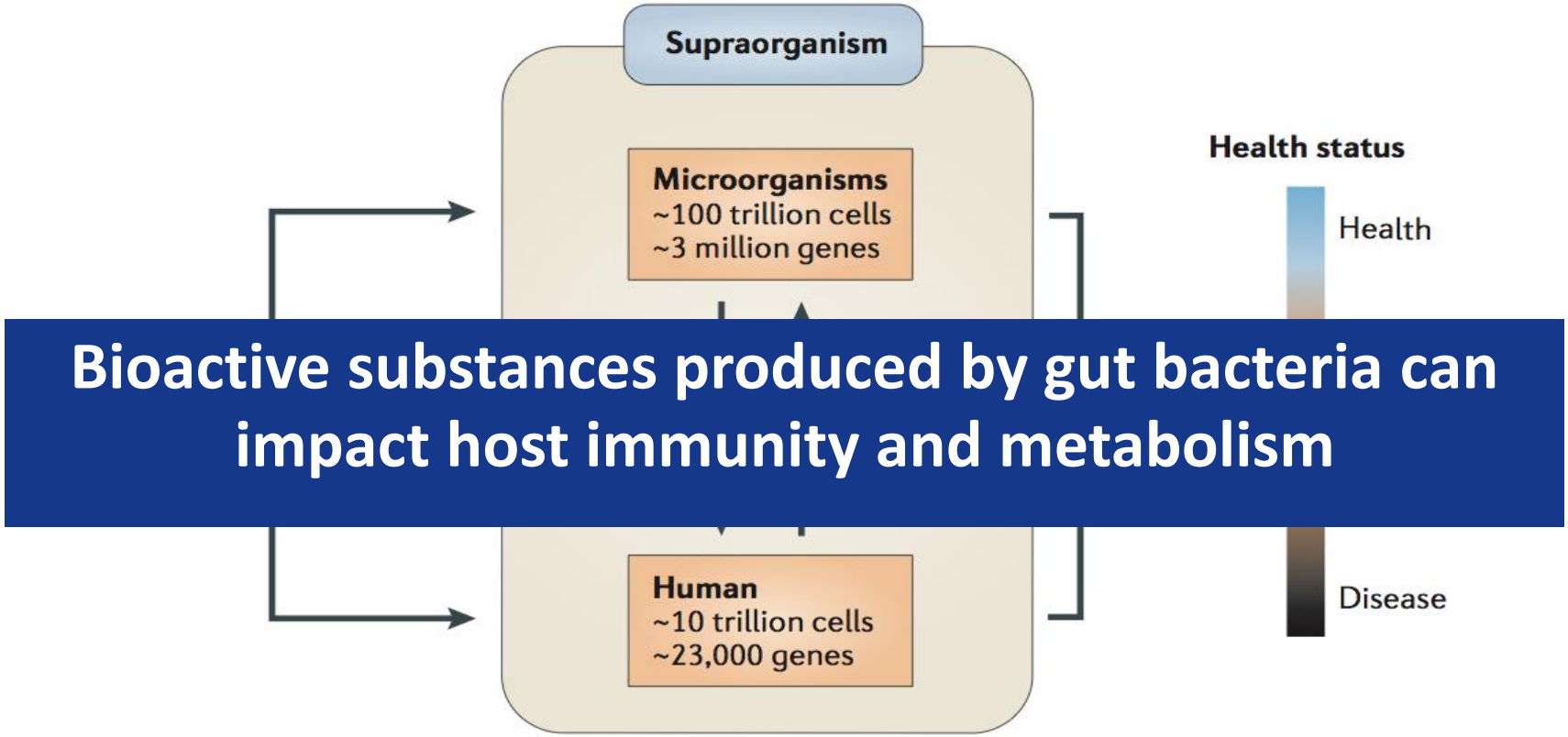
Liping Zhao

Shanghai Jiao Tong University

Rutgers University

Contribution of the gut microbiome to human disease phenome?

微生物组与基因组之间的分子互作影响人体健康表型



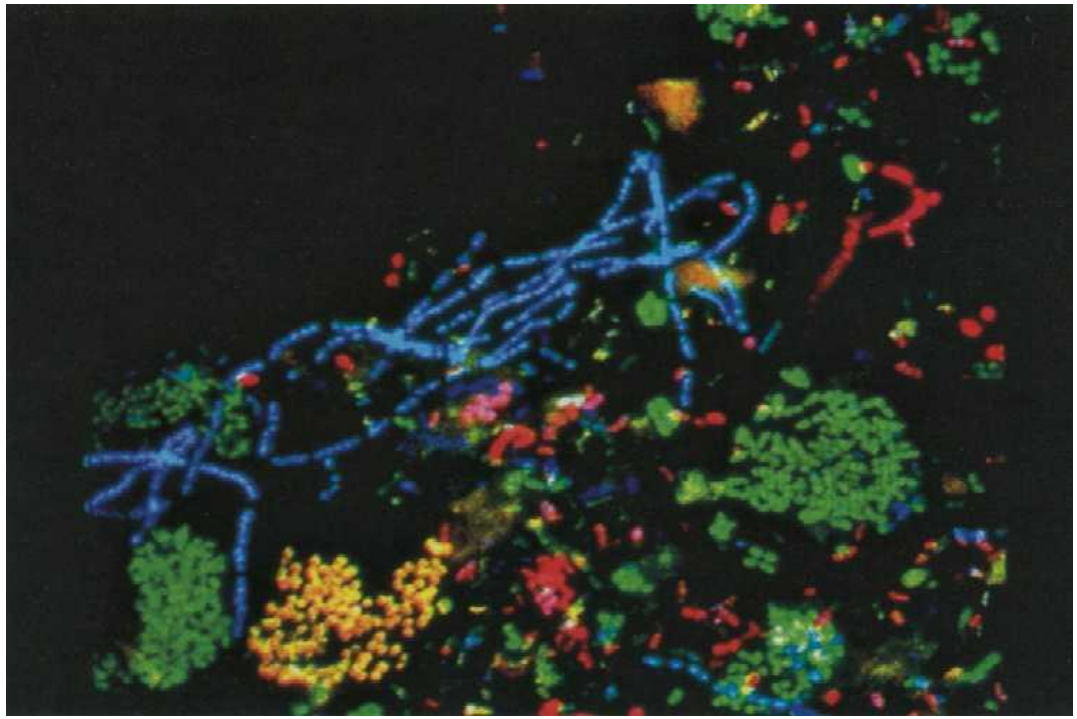
Bioactive substances produced by gut bacteria can impact host immunity and metabolism

Genome + Exposome = Phenome ✗

(Genome + Microbiome) + Exposome = Phenome✓

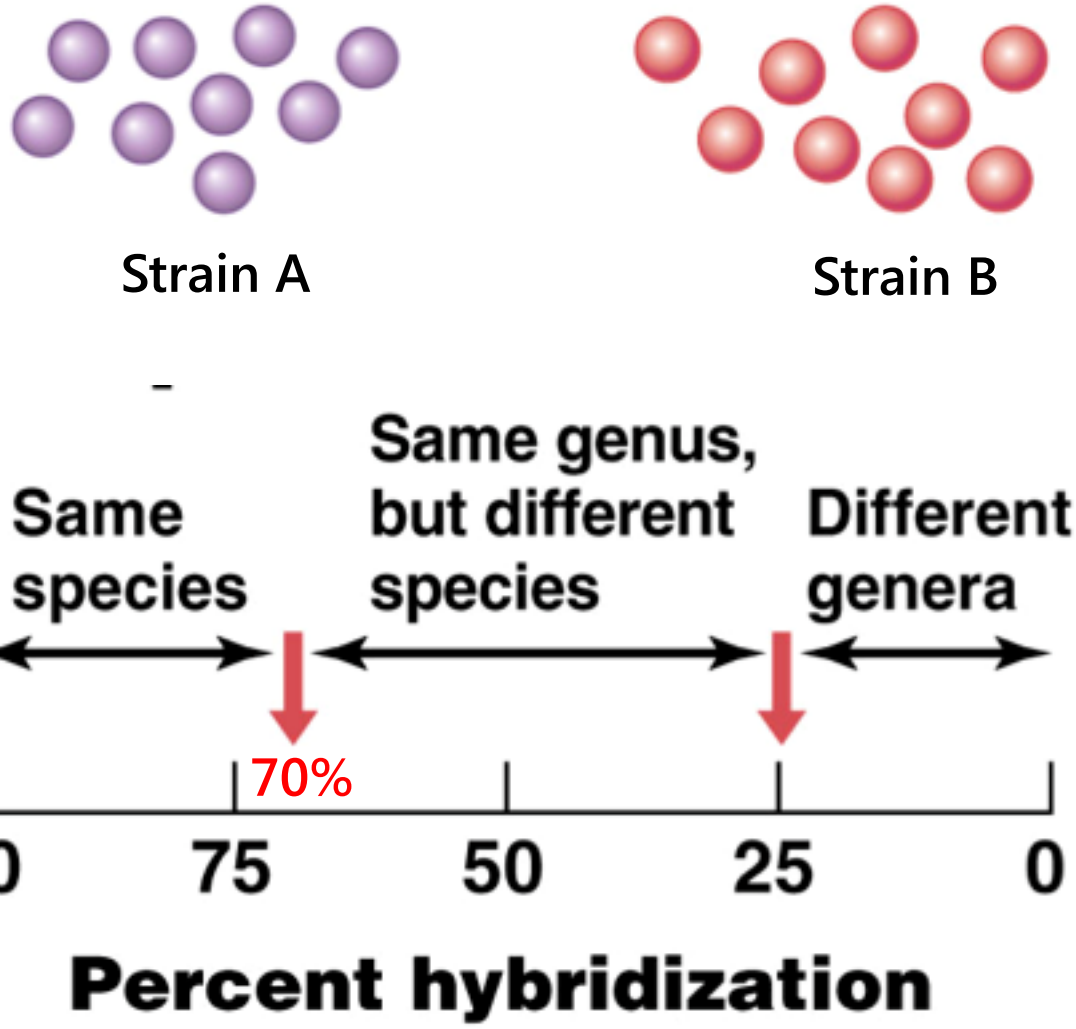
Who are there? Who does What? With Whom? and How?

- Microbial ecologists primarily focus on two areas of study:
  - *Diversities* of microorganisms in nature and how different guilds interact in microbial communities
  - 微生物的多样性
  - *Activities* of microorganisms in nature and monitor their effects on ecosystems
  - 微生物的活性

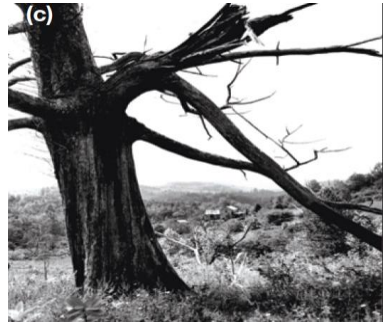


Bacterial functions are strain-specific

- 菌株Strain
- 种Species
- 属Genus
- 科Family
- 目Order
- 纲Class
- 门Phylum
- 界Kingdom
- 域Domain



Not all species are created equal

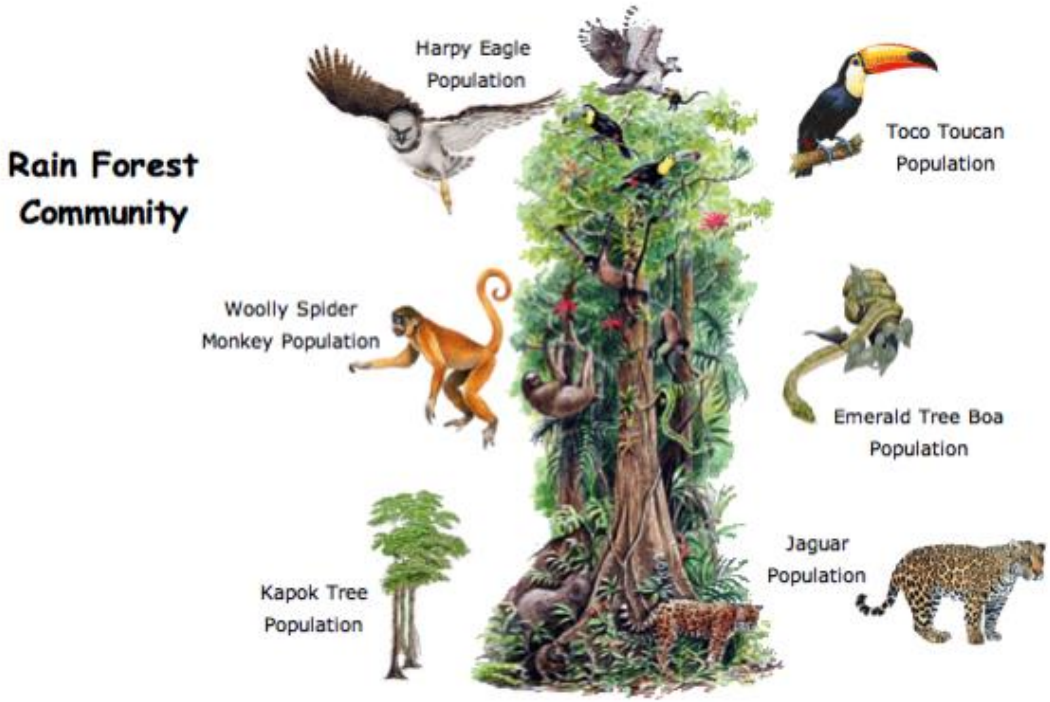


REVIEWS REVIEWS REVIEWS

Loss of foundation species: consequences for the structure and dynamics of forested ecosystems

Aaron M Ellison[1*], Michael S Bank[1], Barton D Clinton[2], Elizabeth A Colburn[1], Katherine Elliott[2], Chelcy R Ford[2], David R Foster[1], Brian D Kloeppel[3], Jennifer D Knoepp[2], Gary M Lovett[4], Jacqueline Mohan[1], David A Orwig[1], Nicholas L Rodenhouse[5], William V Sobczak[6], Kristina A Stinson[1], Jeffrey K Stone[7], Christopher M Swan[8], Jill Thompson[9], Betsy Von Holle[1], and Jackson R Webster[10]

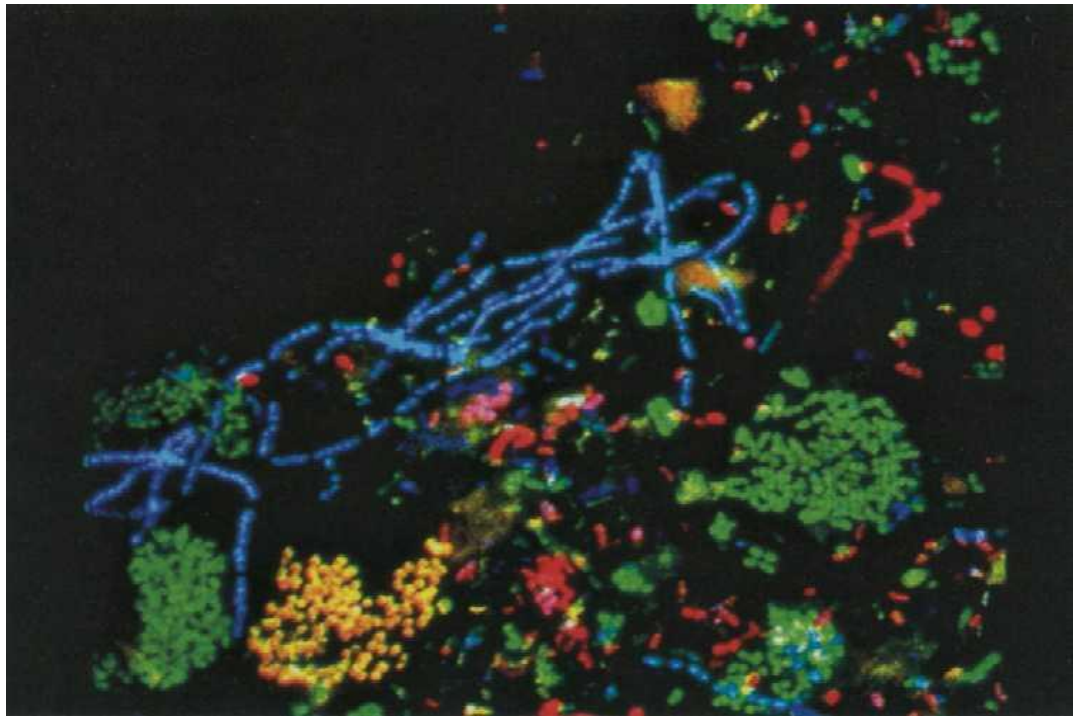
Different species work together as a functional group (guild)



Functional grouping of bacterial species in gut ecosystems=guilds

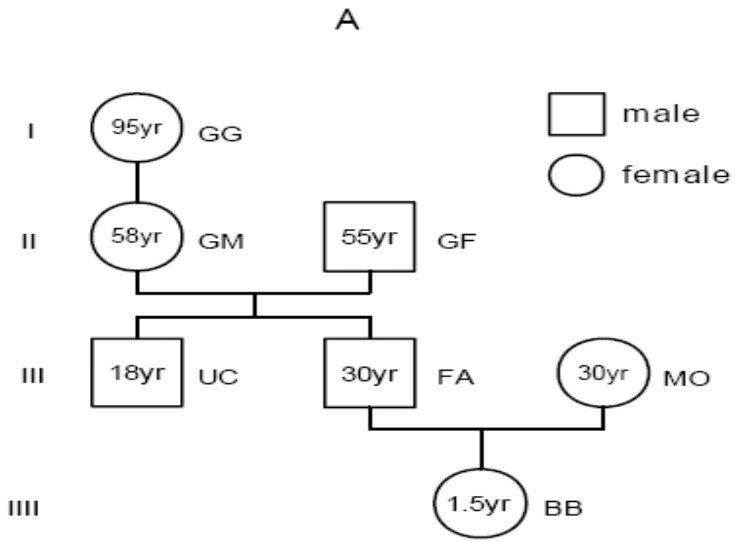
How can we find out who does what in a microbial community?

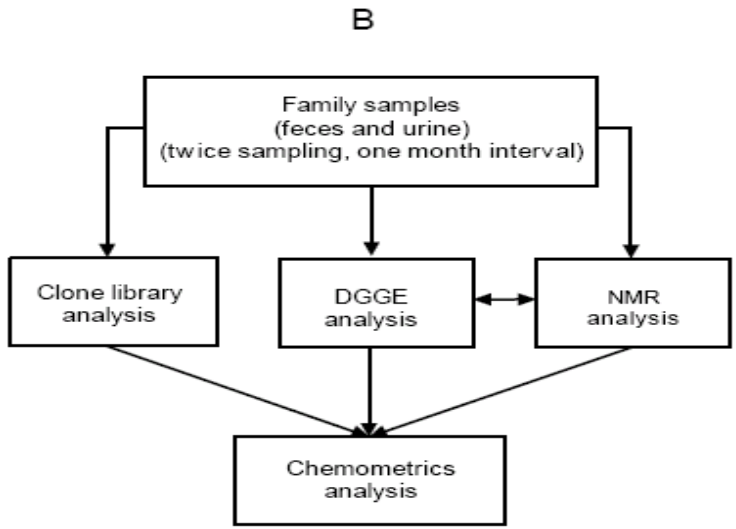
- **Structures vs. Functions**
  - *Diversities* of microorganisms in nature and how different guilds interact in microbial communities
  - 微生物的多样性
  - *Activities* of microorganisms in nature and monitor their effects on ecosystems
  - 微生物的活性

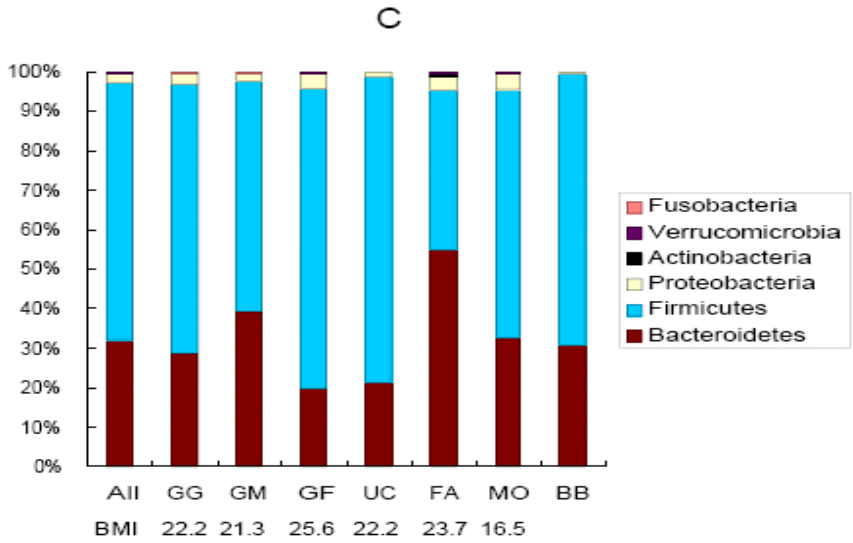


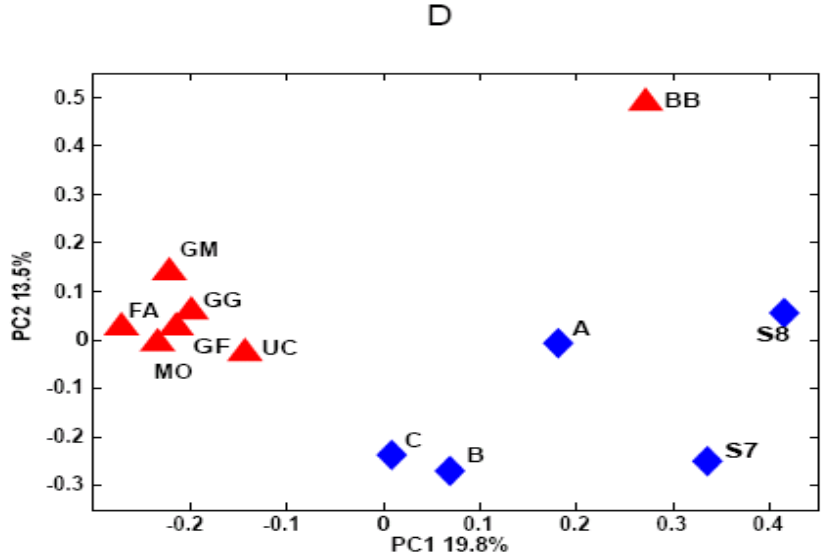
Metagenomics-metabolomics integrated approach

Urine metabolites-gut bacteria correlation analysis
尿液代谢物与肠道细菌的关联分析







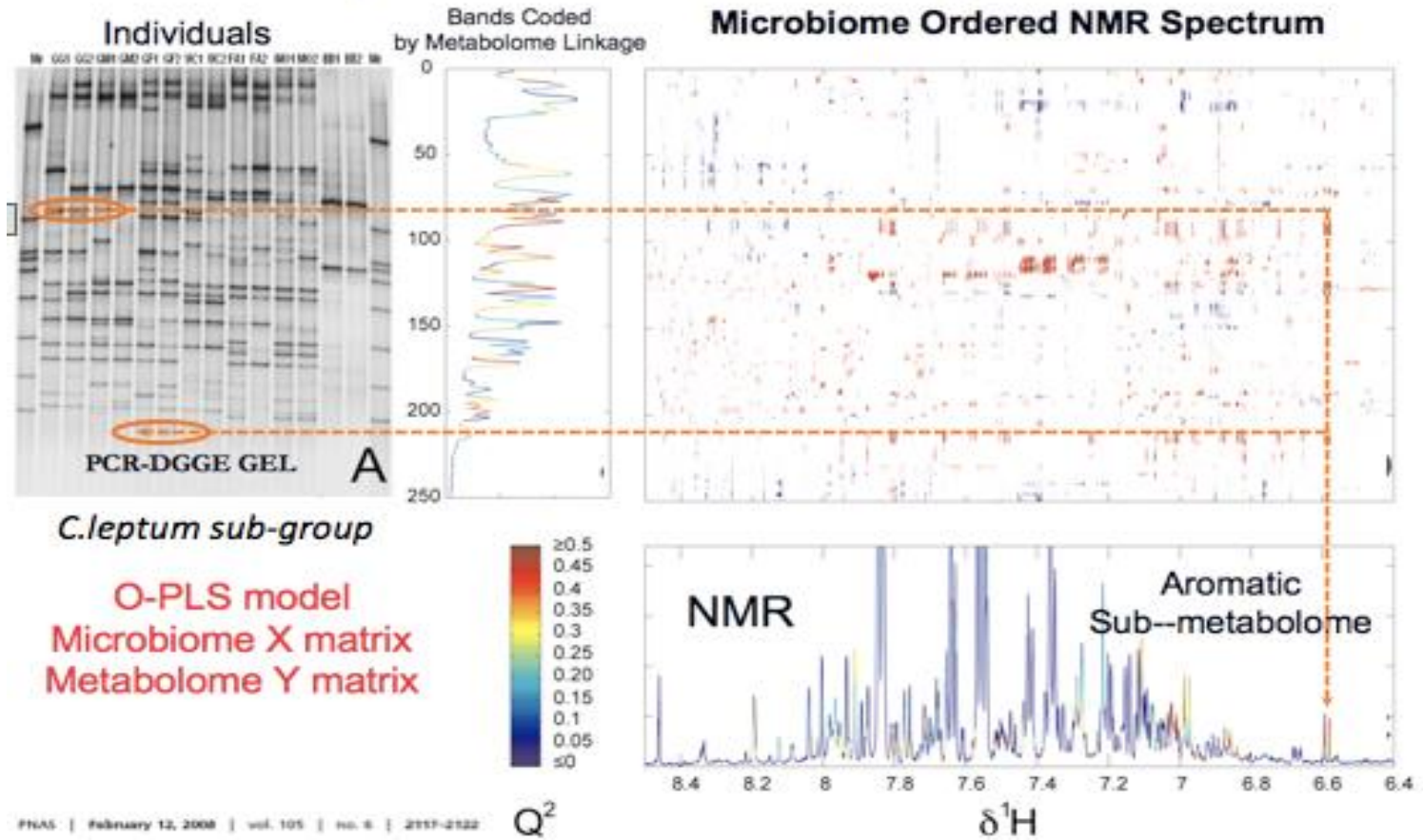


Symbiotic gut microbes modulate human metabolic phenotypes

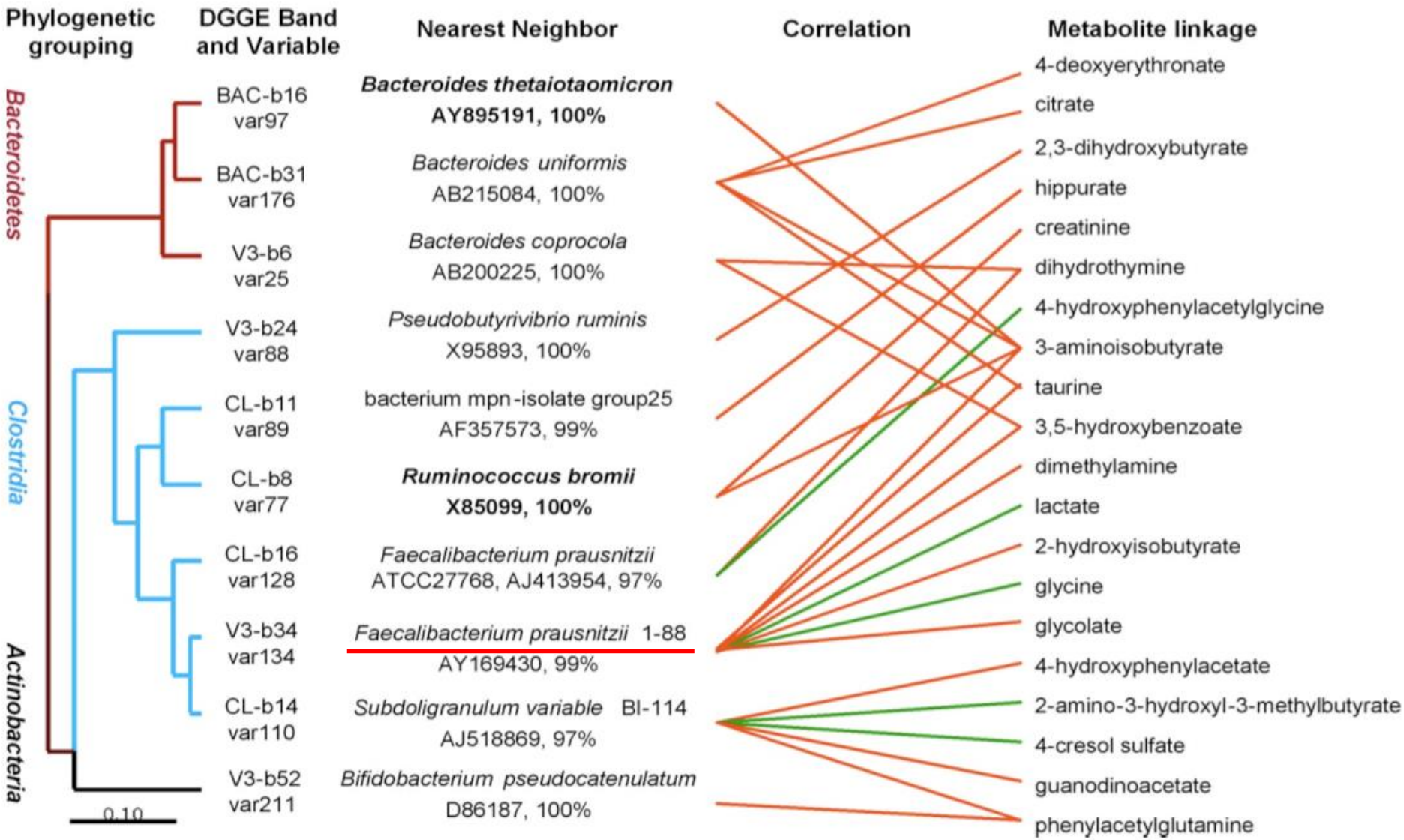
PNAS | February 12, 2008 | vol. 105 | no. 6 | 2117–2122

Min Li*, Baohong Wang†, Menghui Zhang*, Mattias Rantalainen‡, Shengyue Wang§, Haokui Zhou*, Yan Zhang*, Jian Shen*, Xiaoyan Pang*, Meiling Zhang*, Hua Wei*, Yu Chen†, Haifeng Lu†, Jian Zuo†, Mingming Su*, Yunping Qiu*, Wei Jia*, Chaoni Xiao¶‖, Leon M. Smith‡, Shengli Yang*, Elaine Holmes‡, Huiru Tang¶**, Guoping Zhao§**, Jeremy K. Nicholson‡**, Lanjuan Li†**, and Liping Zhao*,**

Statistical spectroscopic linkage of microbial genomics and speciation data with metabolic profiles



Urine metabolites-gut bacteria correlation analysis
尿液代谢物与肠道细菌的关联分析



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nature REVIEWS MICROBIOLOGY

Research Highlight

Nature Reviews Microbiology **6**, 256-257 (April 2008) | doi:10.1038/nrmicro1880

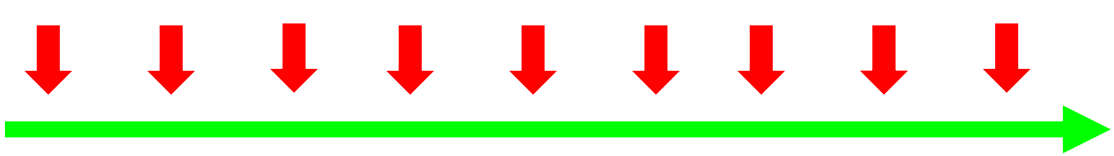
Symbiosis: Who does what in the microbiome?

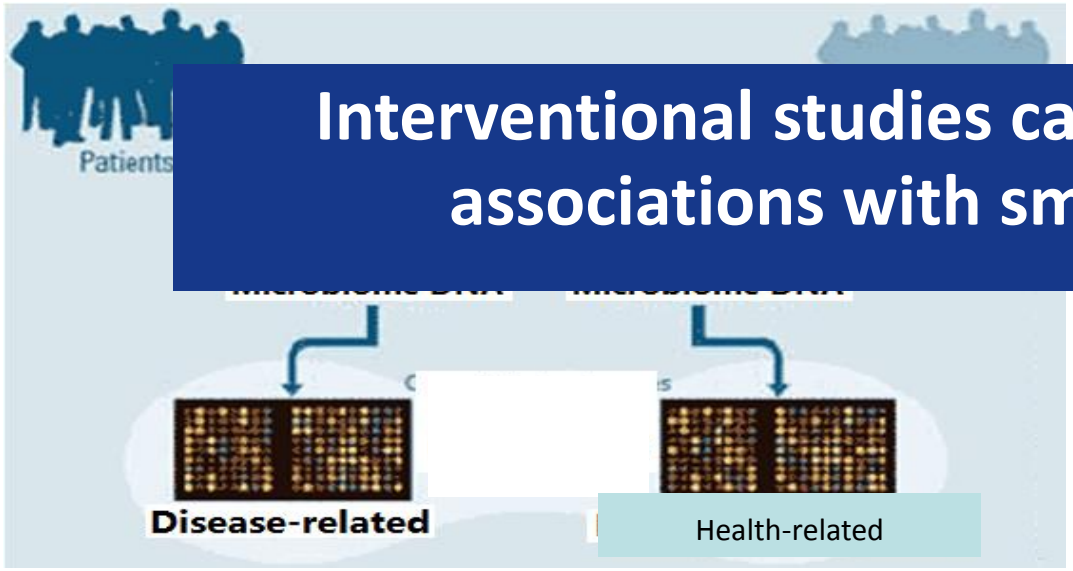
Susan Jones

Recent studies have shown that the complement of gut bacteria varies among individuals, but specific data linking the bacteria present to their functions in human physiology have been lacking. In a recent report, Min Li and colleagues describe a multidisciplinary approach to link the functions of the trillions of microbial gut bacteria — the human microbiome — to host metabolic phenotypes.

Interventional Clinical Study-based MiWAS
基于临床干预的全微生物组关联分析

Interventional Study, time series sampling





Interventional studies can lead to high quality associations with smaller sample size

adapted from Human Genome Project and The Metagenomics Group at CBS

Eat for Health, Food as medicine
-孙思邈，Simiao Sun

- 胃肠乃后天之本
- Gut is the foundation for health, which is acquired after birth.
  - -TCM tenet
- “使米脂入腹，莫使酒脂入肠”
- “Let essence of plant nutrition get into your lower gut, not the animal nutrition”

What are the key food ingredient -Traditional Chinese Medicinal Food list (MOH)

- Dietary fibers-complex carbohydrates

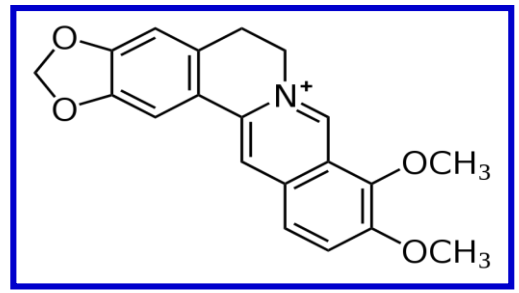
- Natural, wholesome grains, processed in a way to have low bioavailability of carbohydrates to human and high availability to gut microbiota for promoting production of short chain fatty acids.

What are the key food ingredient -Traditional Chinese Medicinal Food list (MOH)

- Phytochemicals, which are not absorbed into blood stream nor metabolized by gut bacteria, can modulate gut microbiota in a way to promote SCFAs producers and reduce endotoxin producers.

- Phytochemicals
  - ➥Bitter compounds

Berberis

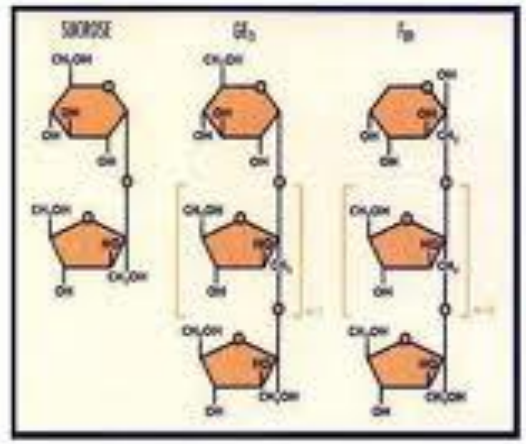


Berberine

Bitter melon

Dietary modulation of gut microbiota for obesity control
以肠道菌群为靶点的肥胖症营养干预

▶ “Feed me, feed my bacteria”



Whole grains, traditional Chinese medicine and prebiotics (WTP diet)

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journal homepage: www.ebiomedicine.com

Dietary Modulation of Gut Microbiota Contributes to Alleviation of Both Genetic and Simple Obesity in Children☆

Chenhong Zhang [a,1], Aihua Yin [b,1], Hongde Li [c,1], Ruirui Wang [a,1], Guojun Wu [a,1], Jian Shen [a,1], Menghui Zhang [a], Linghua Wang [a], Yaping Hou [b], Haimei Ouyang [b], Yan Zhang [b], Yinan Zheng [b], Jicheng Wang [b], Xiaofei Lv [b], Yulan Wang [c], Feng Zhang [a], Benhua Zeng [d], Wenxia Li [d], Feiyan Yan [a], Yufeng Zhao [a], Xiaoyan Pang [a], Xiaojun Zhang [a], Huaqing Fu [a], Feng Chen [a], Naisi Zhao [a], Bruce R. Hamaker [a,j], Laura C. Bridgewater [a,j], David Weinkove [k], Karine Clement [h], Joel Dore [g], Elaine Holmes [e], Huasheng Xiao [l], Guoping Zhao [l], Shengli Yang [a], Peer Bork [f], Jeremy K. Nicholson [e], Hong Wei [d], Huiru Tang [c,*], Xiaozhuang Zhang [b,*], Liping Zhao [a,*]

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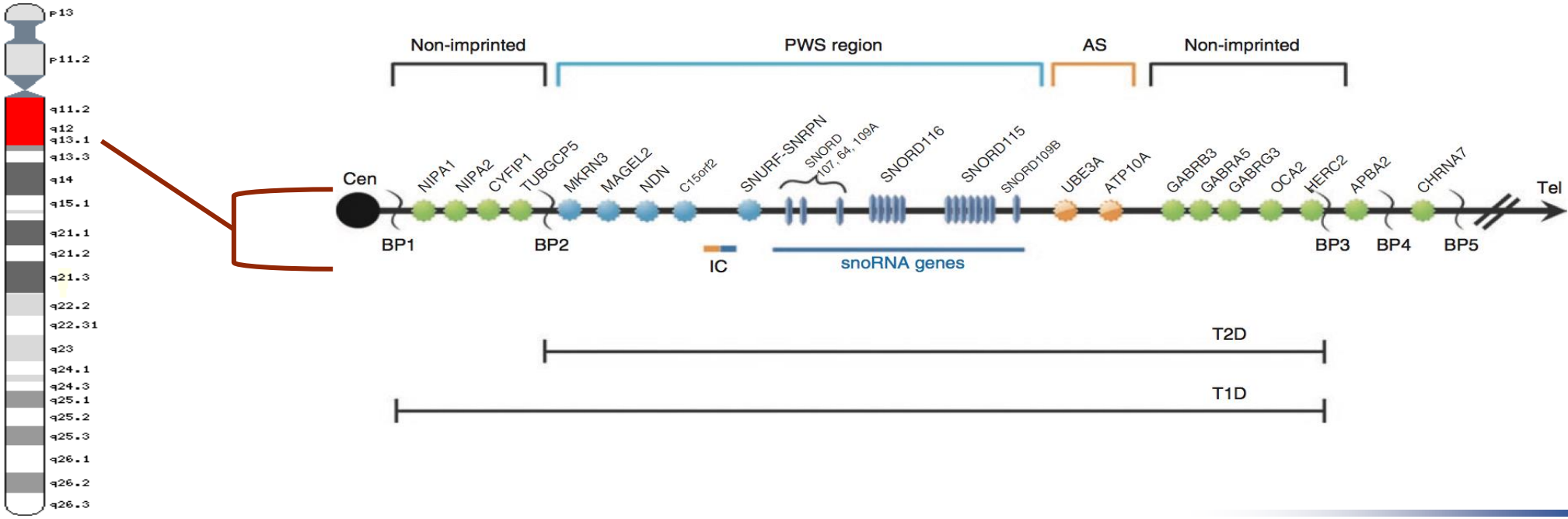
Prader-Willi syndrome (PWS) – a genetic defect disease “小胖伟利”

Prader-Willi syndrome is due to absence of paternally expressed imprinted genes at 15q11.2-q13.

- **Paternal deletion of this region (65–75%)**
- **Maternal uniparental disomy 15 (20–30%)**
- **An imprinting defect (1–3%)**

Paternal No. 15 chromosome



Prader-Willi syndrome (PWS)

Early Infancy

- Hypotonia
- Hypogonadism
- Feeding difficulties

Childhood

- Hyperphagia *(feel constant hunger and continuous food-seeking)*
  ➔ **Morbid obesity**
- Cognitive disability
- Behavioral problems

Adulthood

- Weight control
  ➔life quality improvement
  ➔life expectancy prolongation

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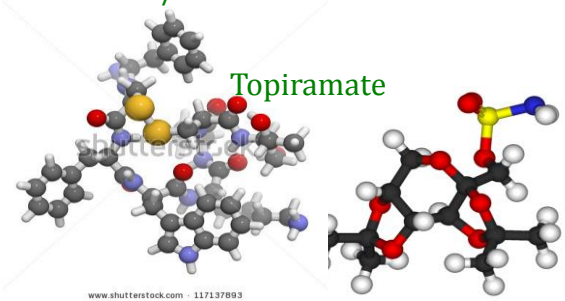
Method for PWS Weight Control

Anorexigenic Drugs

Somatostatin / Octreotide

Topiramate

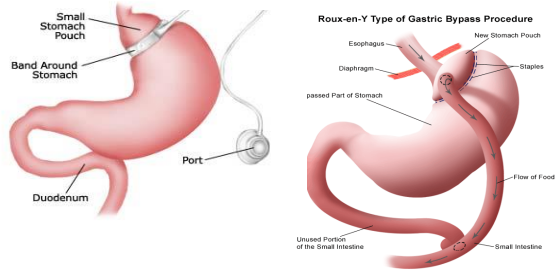


Not effectively suppress appetite
Not reduce body weight

Surgery

Gastric banding

Gastric bypass



High disability and mortality rate
High incidence of post-operation complications

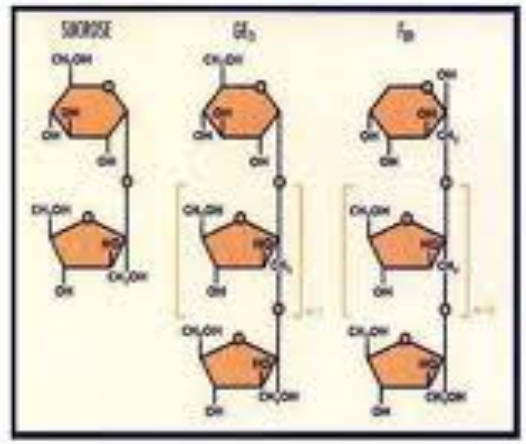
Low-calorie diets

Difficult to follow by PWS with hyperphagia

There is no particularly effective and safe medical methods to control PWS-associated obesity and hyperphagia

WTP Diet intervention of PWS

- Subjects: Obese PWS Children
  - Dietary intervention
    - In hospital

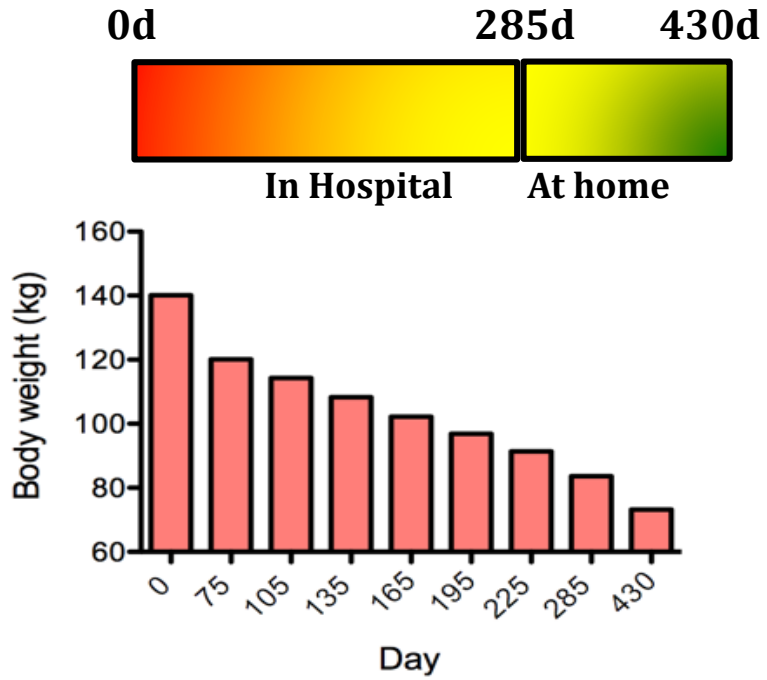


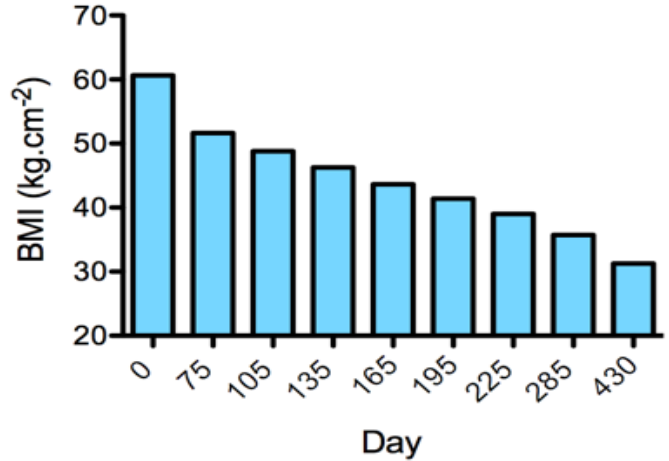
Whole grains, traditional Chinese medicine and prebiotics (WTP diet)

One of the PWS children （GD02) in our clinical study

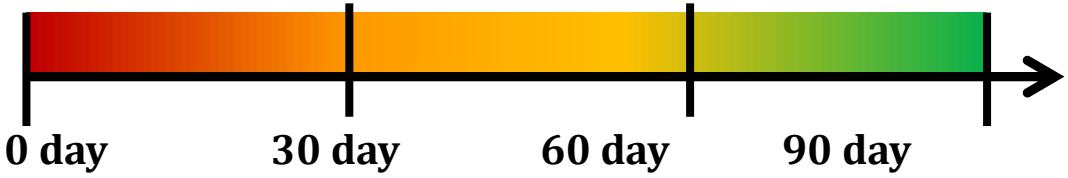
14 years old male

	Before intervention	285 day of intervention
Weight	140.1kg	83.6kg
BMI	60.6 kg.cm^{-2}	35.7 kg.cm^{-2}
Height	152cm	153cm

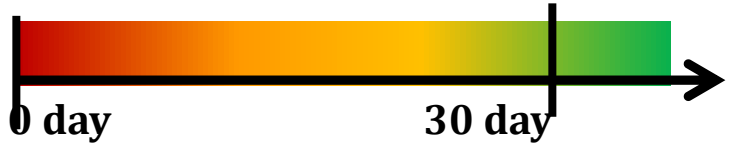




The PWS (n=17) and Simple obesity(SO, n=21) cohorts



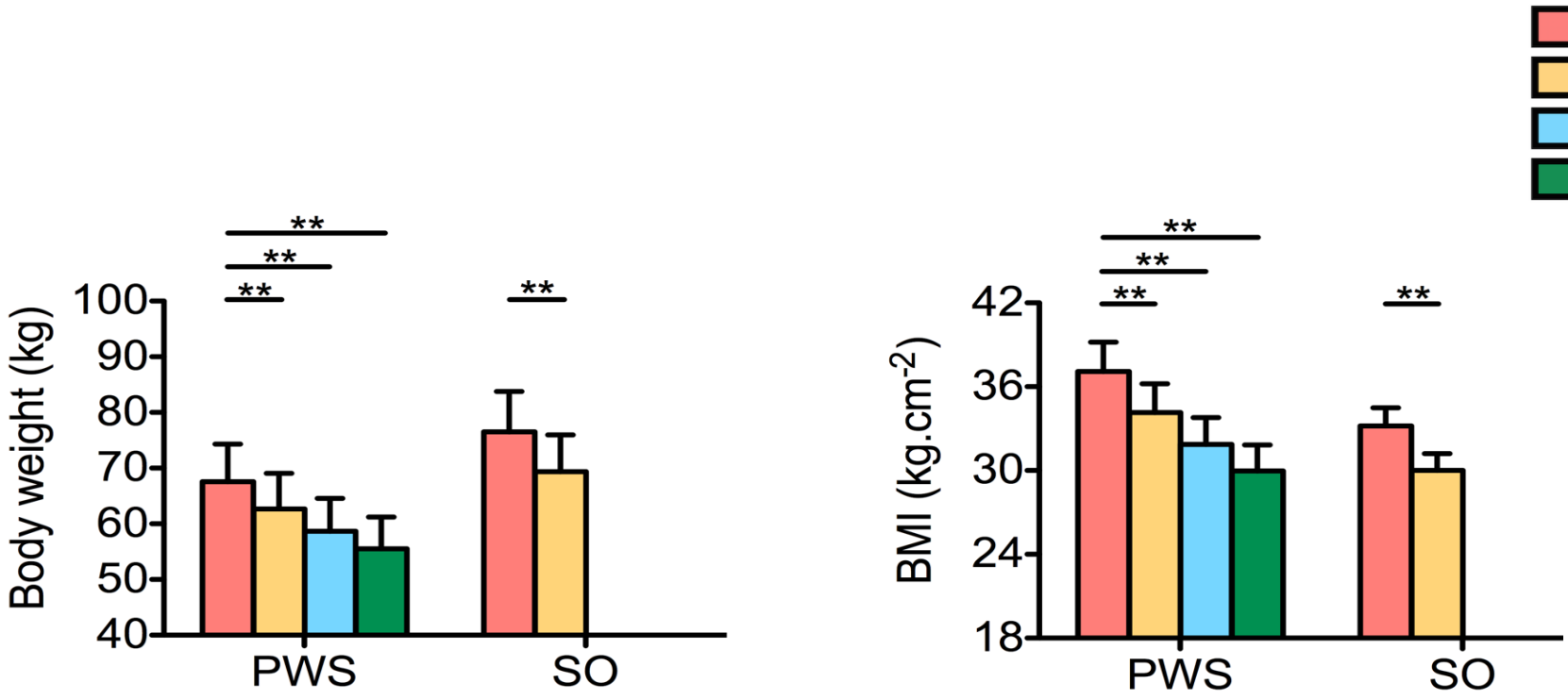
Number	Disease	Gender	Age
GD02	PWS	male	14
GD03	PWS	male	16
GD04	PWS	male	5
GD12	PWS	female	8.5
GD15	PWS	male	13
GD18	PWS	male	7
GD39	PWS	male	6
GD40	PWS	male	15
GD41	PWS	male	6
GD42	PWS	male	5
GD43	PWS	male	8
GD47	PWS	female	12
GD50	PWS	male	5
GD51	PWS	female	8
GD52	PWS	female	12
GD58	PWS	male	8
GD59	PWS	male	9



Number	Disease	Gender	Age
GD05	obese	female	10
GD06	obese	female	4
GD08	obese	female	6
GD10	obese	male	3
GD11	obese	female	4
GD13	obese	female	12
GD17	obese	female	4
GD20	obese	male	16
GD21	obese	male	14
GD23	obese	female	8
GD24	obese	female	5
GD26	obese	male	15
GD28	obese	male	16
GD29	obese	female	8
GD31	obese	female	15
GD32	obese	male	14
GD33	obese	male	14
GD35	obese	female	9
GD36	obese	female	15
GD54	obese	male	16
GD56	obese	female	13

Dietary intervention improved Body weight and BMI in PWS and SO children

体重下降



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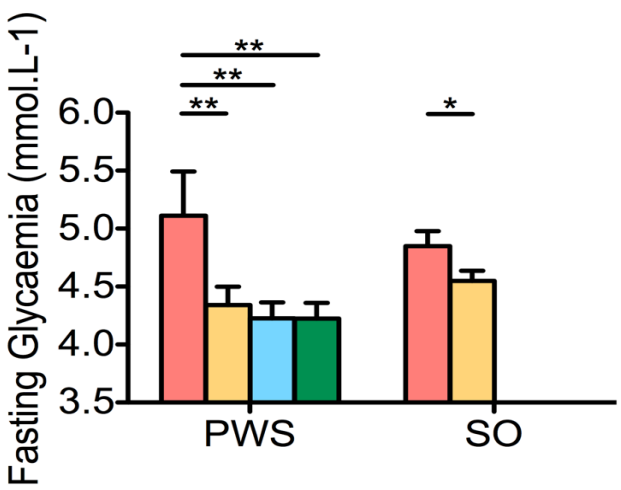
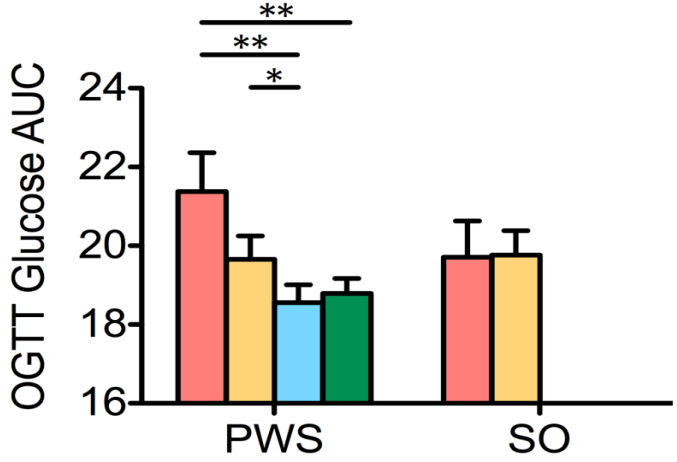
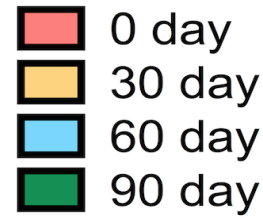
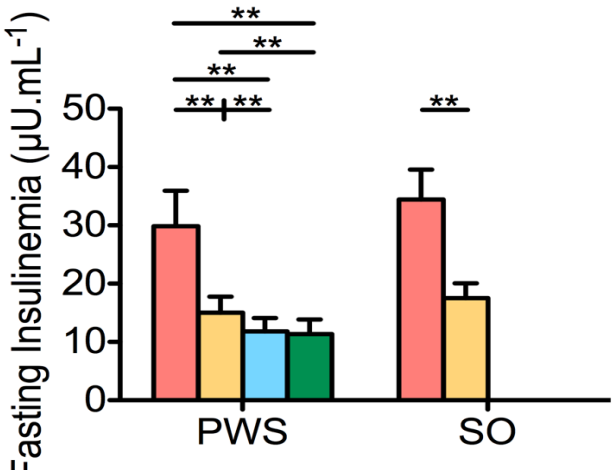
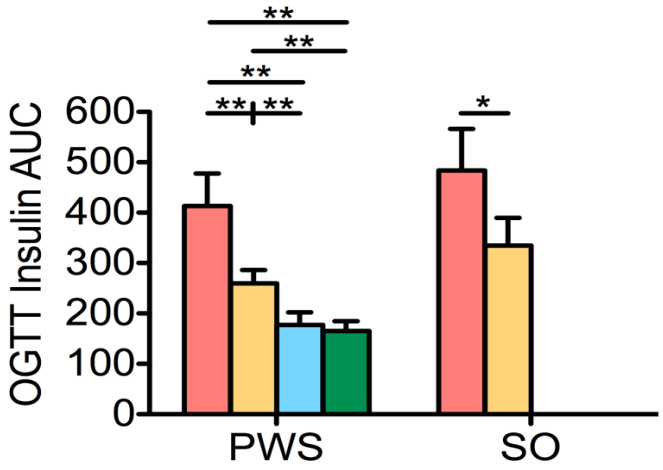
Dietary intervention improved plasma glucose homeostasis in PWS and obese children
糖代谢改善

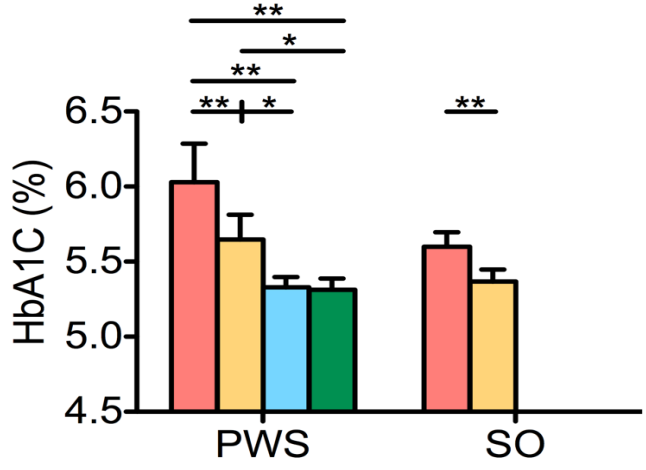












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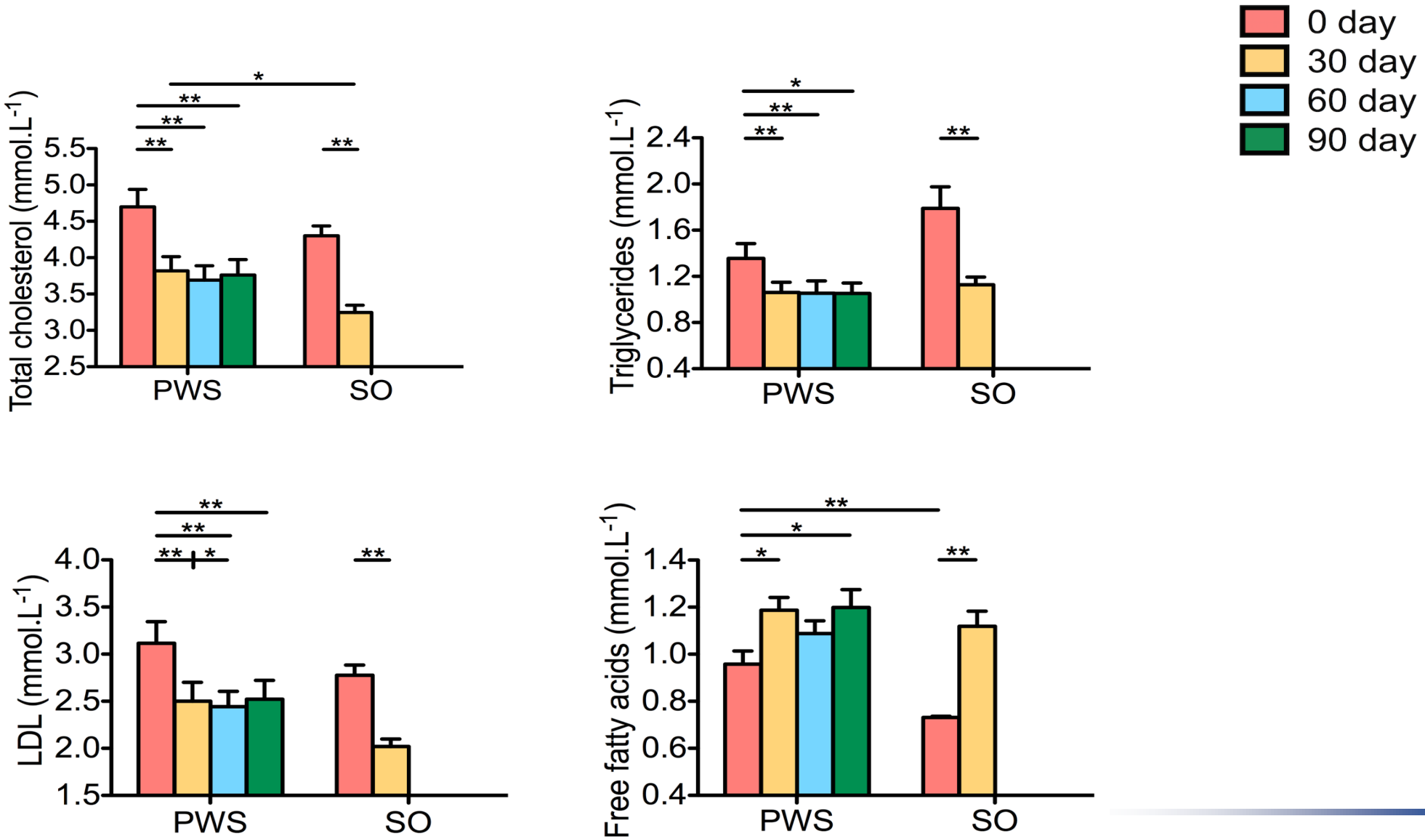
Dietary intervention improved plasma lipid homeostasis in PWS and obese children
脂代谢改善



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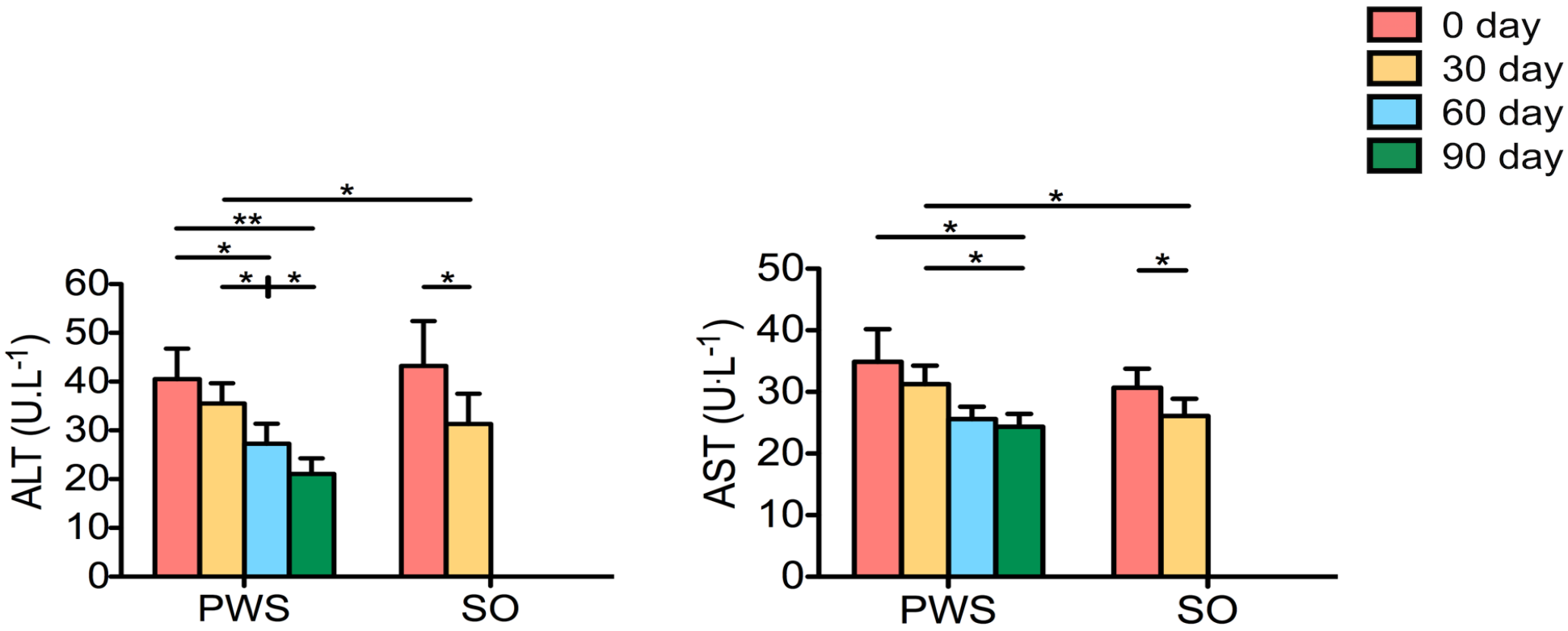
Dietary intervention improved hepatic function markers in PWS and obese children
肝功能改善



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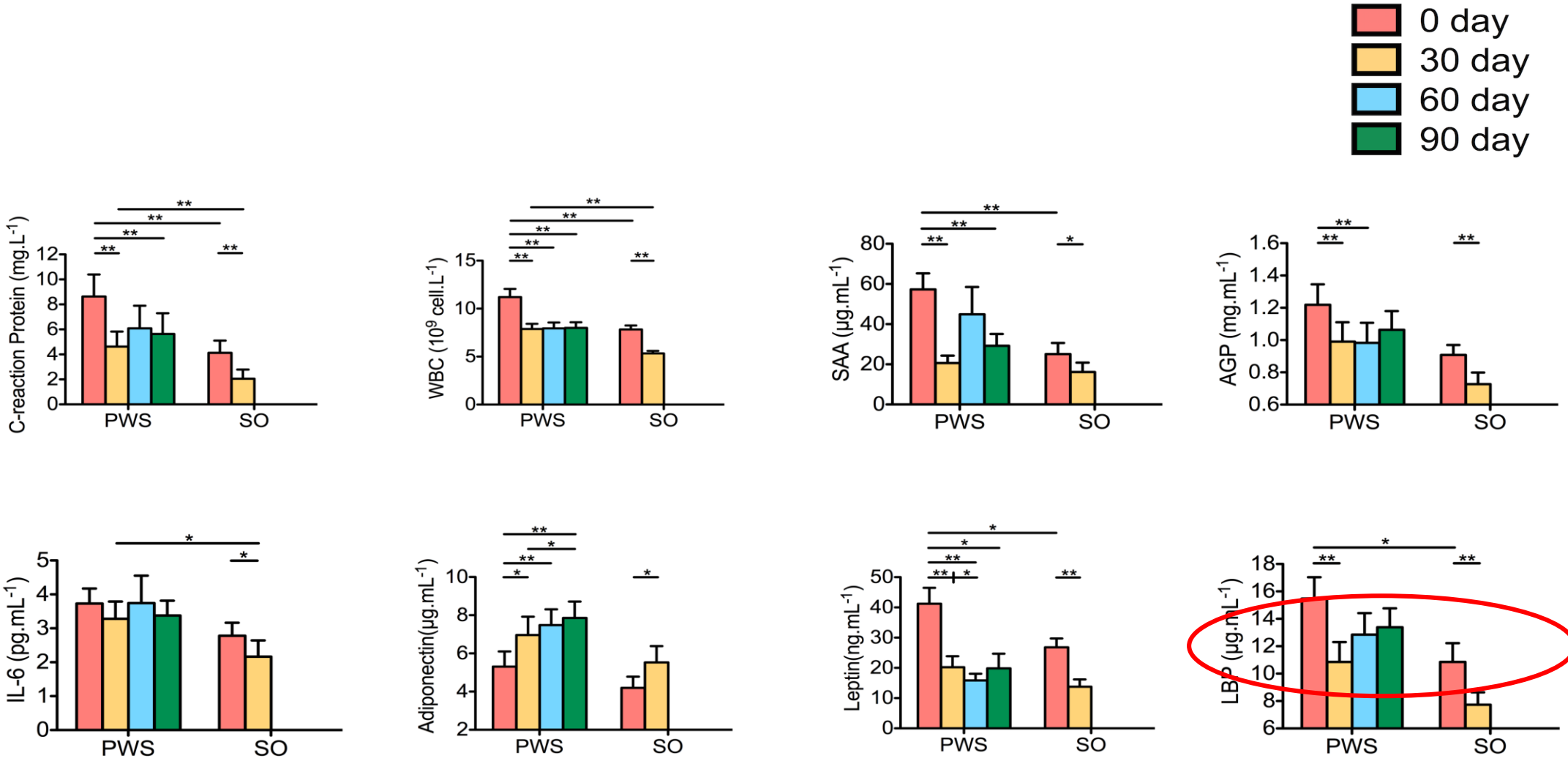
Dietary intervention improved inflammation related markers in PWS and obese children

炎症改善



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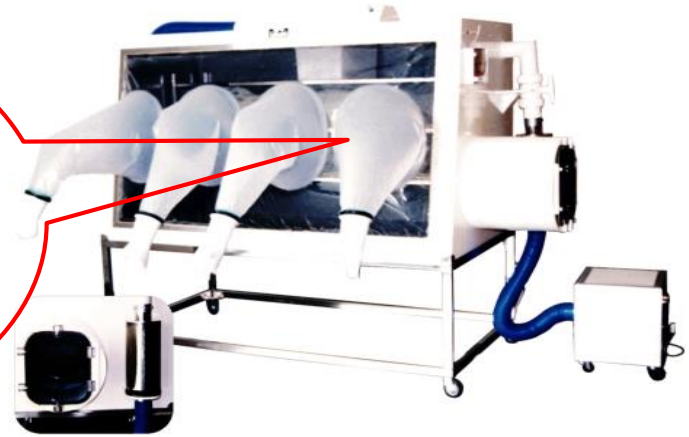
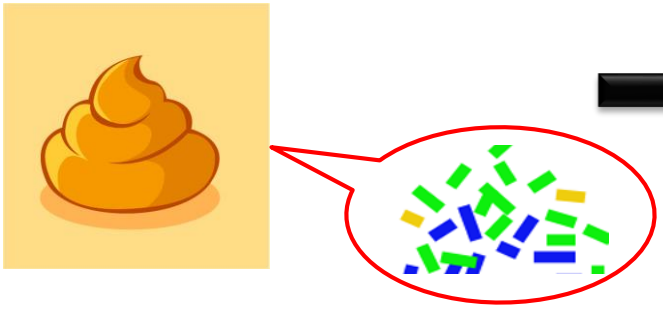
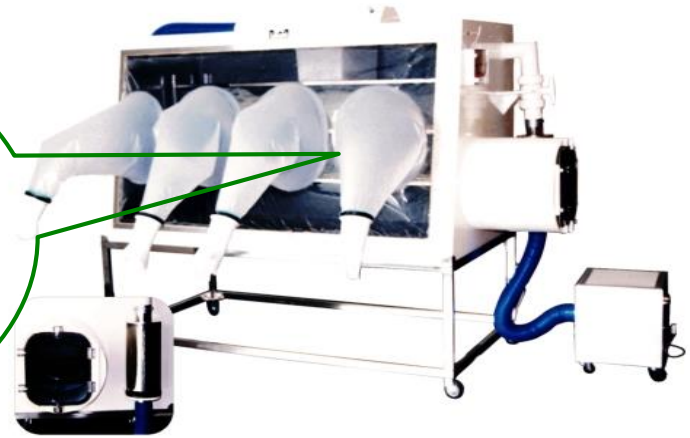
Transplanted with PWS gut microbiota
菌群移植

PWS Fecal bacteria before intervention



PWS Fecal bacteria at the end of intervention

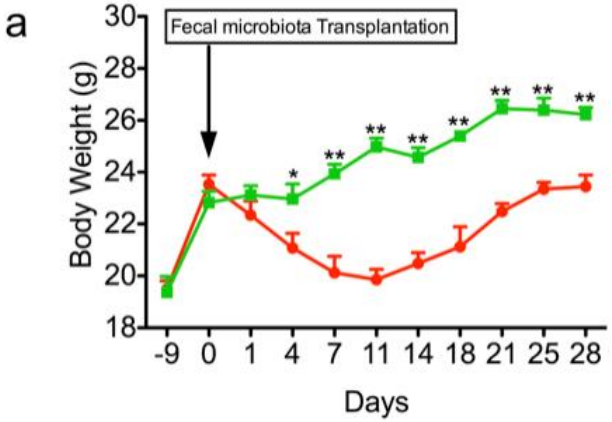


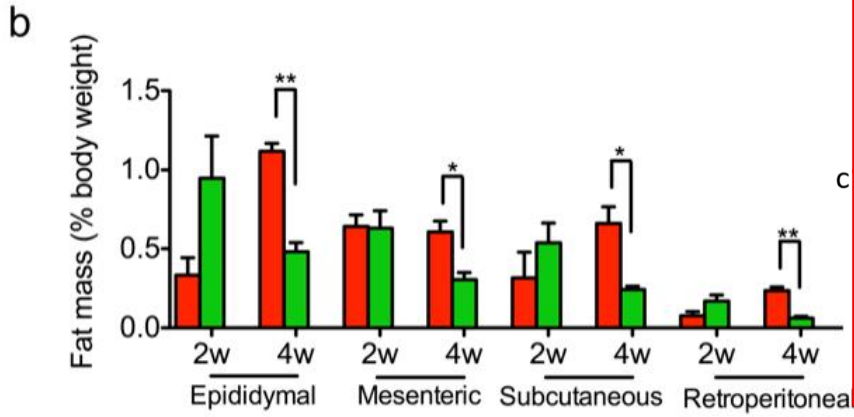


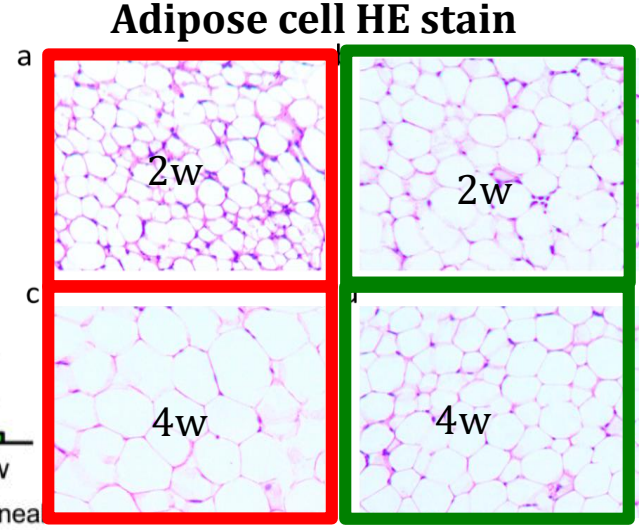
Impaired metabolism of gnotobiotic mice transplanted with PWS gut microbiota

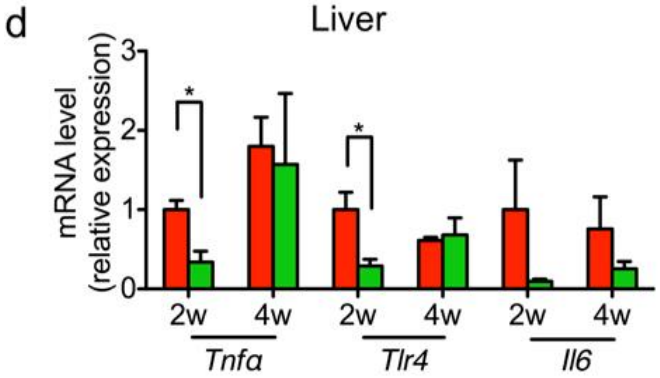
Gnotobiotic mice
Received microbiota from PWS
before intervention

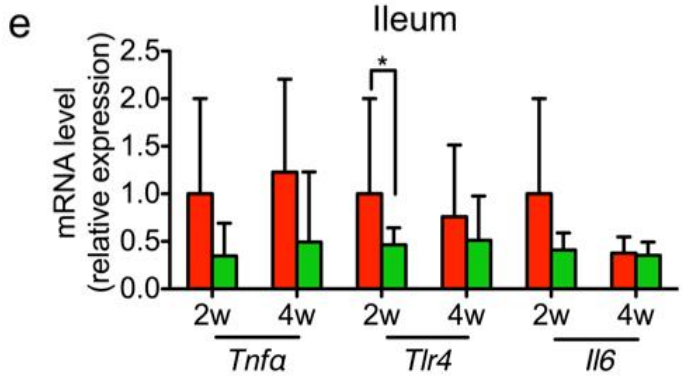
Gnotobiotic mice
Received microbiota from PWS after intervention

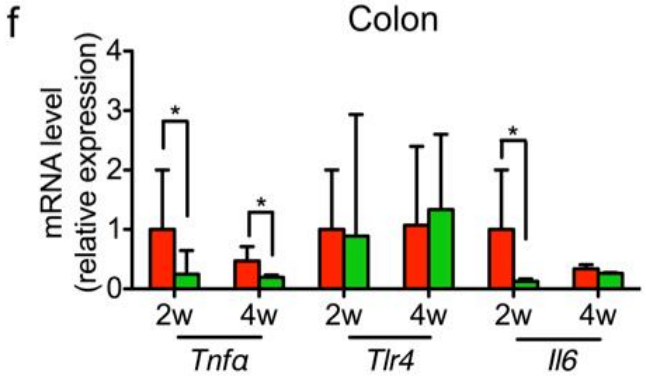




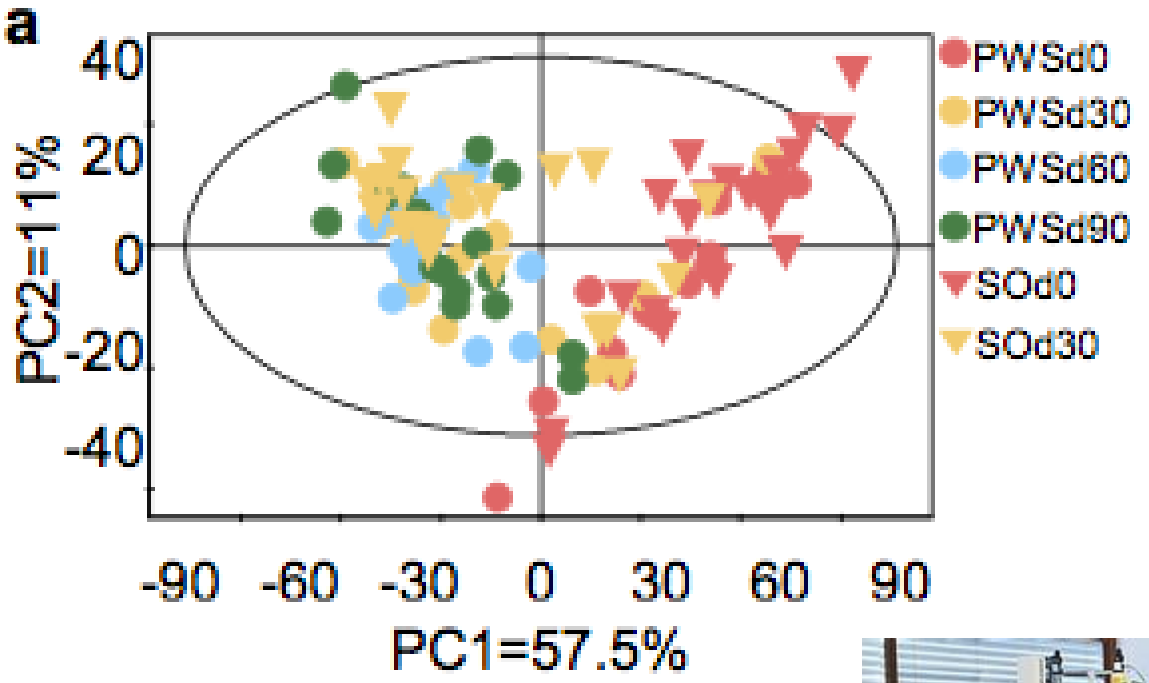


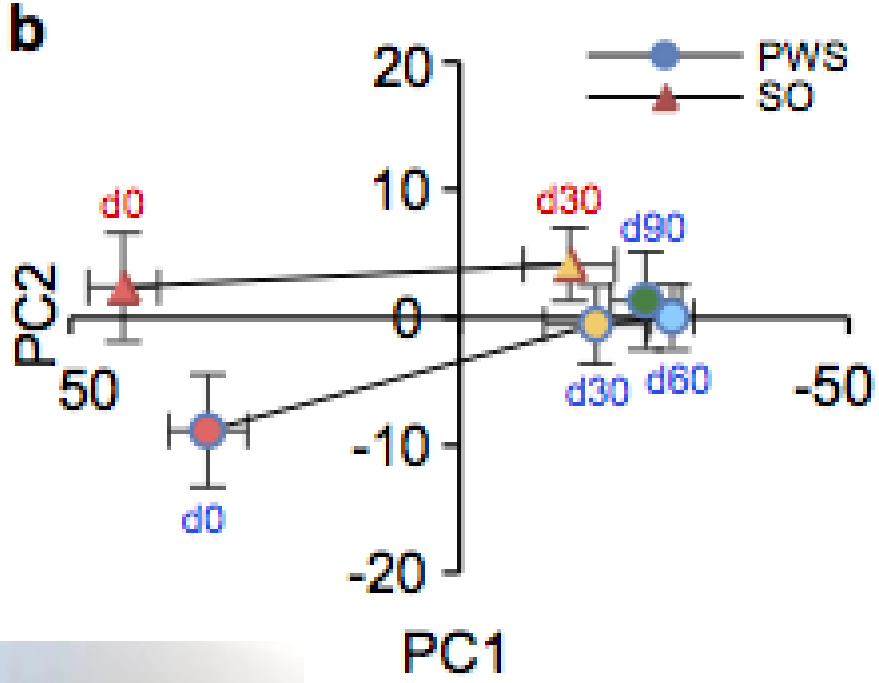




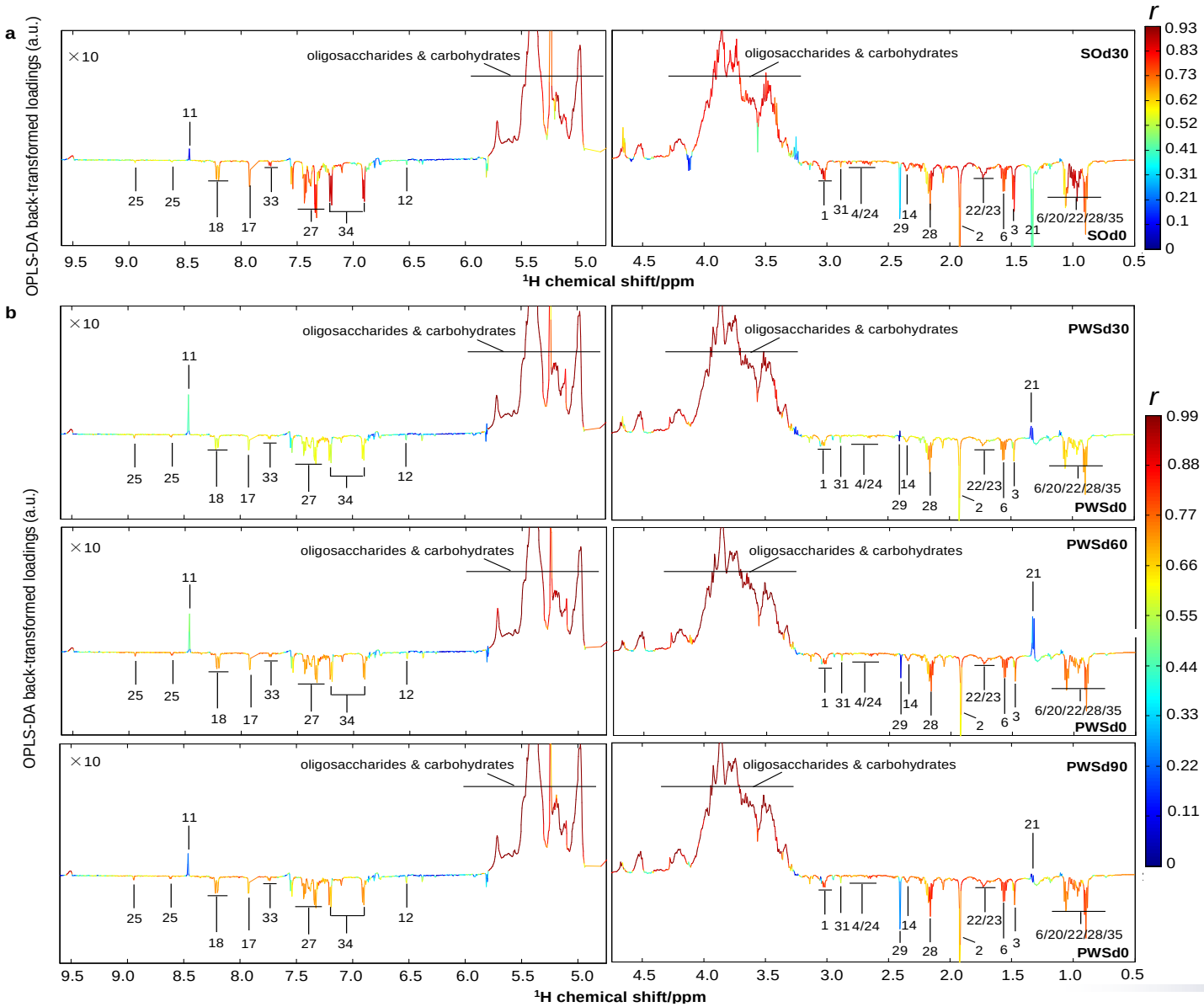


NMR-based metabolomic profiling of fecal water samples
粪便提取液的代谢物组成变化

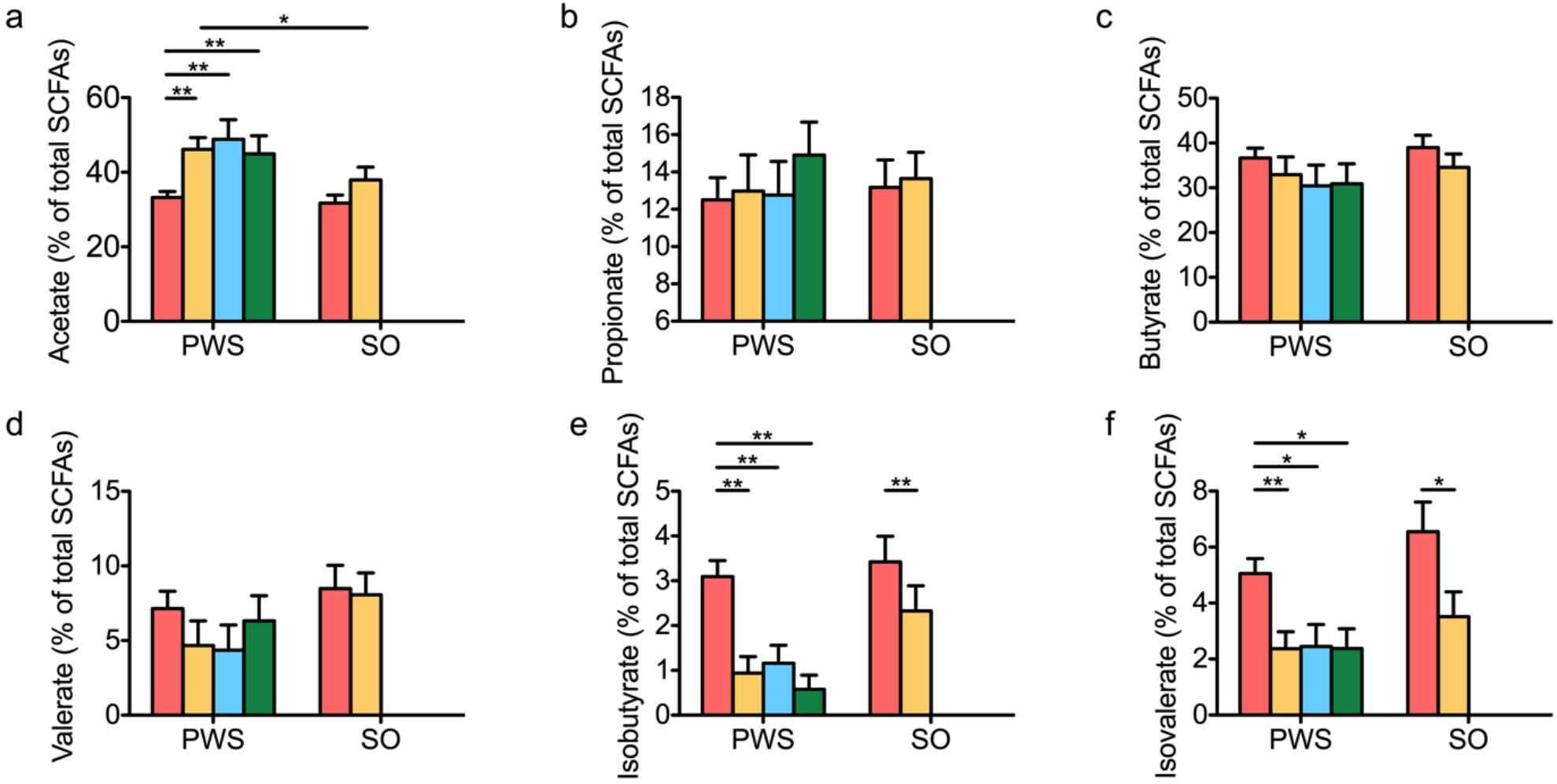




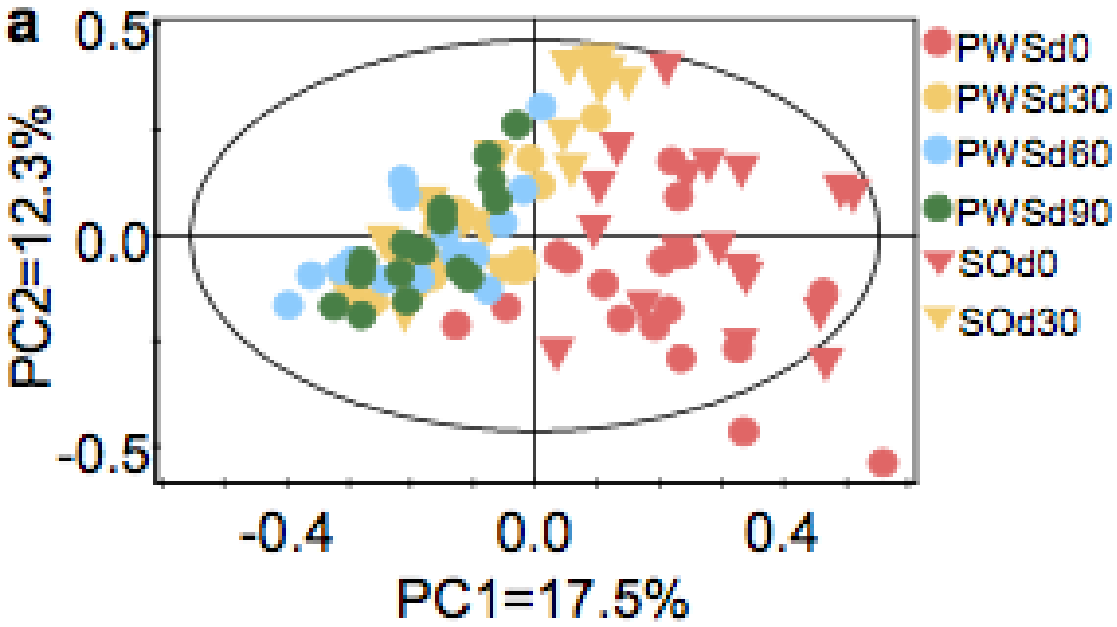
The increase of non-digestible carbohydrates and decrease of aromatic amino acids and bacterial metabolites

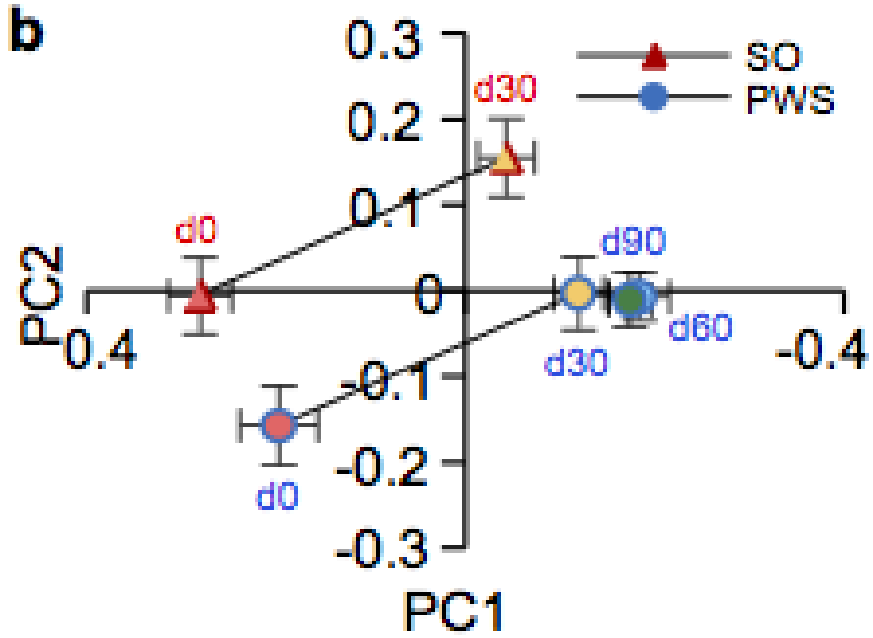


The changes of relative concentrations of SCFAs in PWS and SO subjects
短链脂肪酸的变化

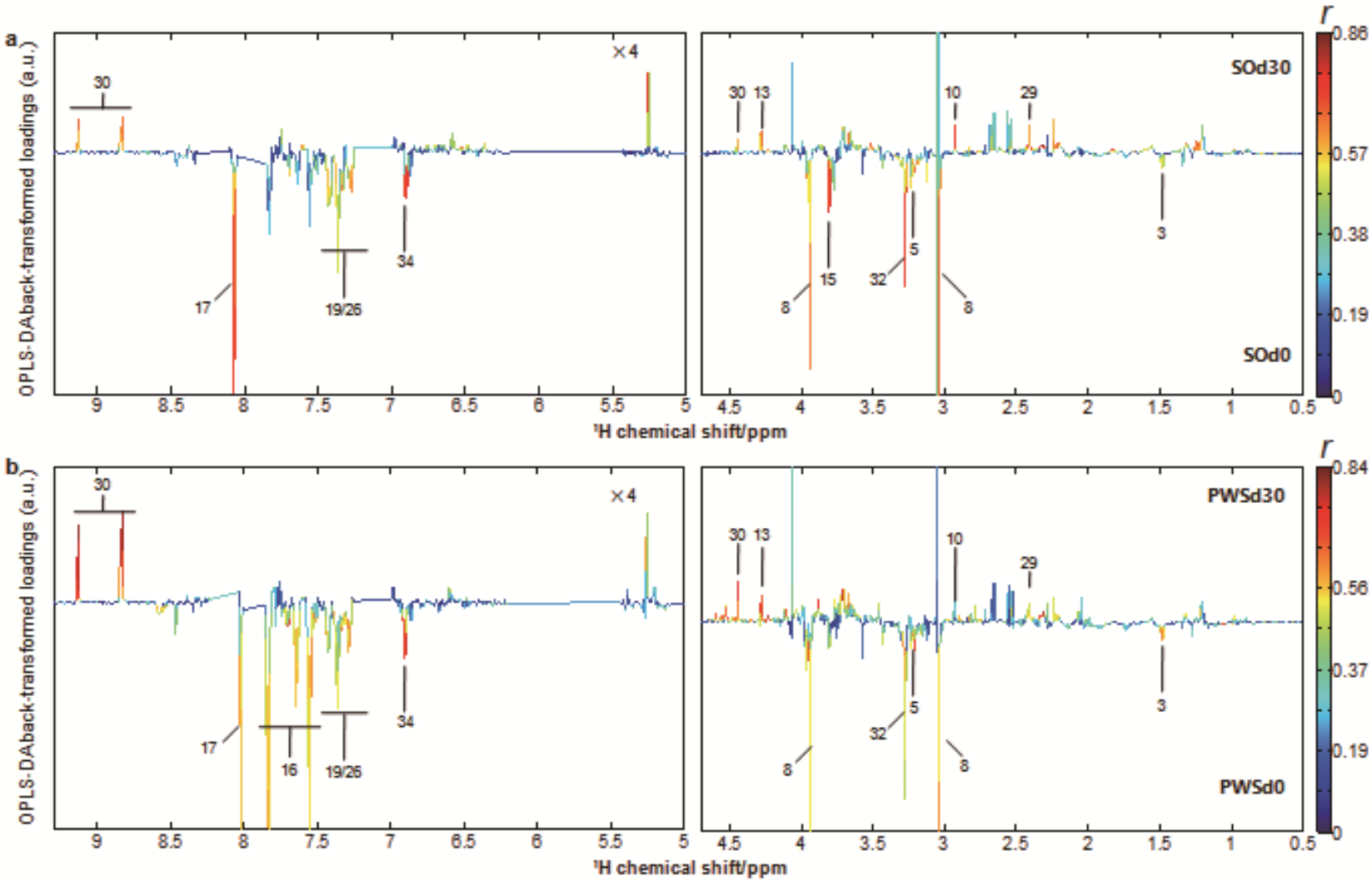


NMR-based metabolomic profiling of urine samples
尿液代谢物组成的变化





Changes of urine metabolites during intervention in PWS and SO

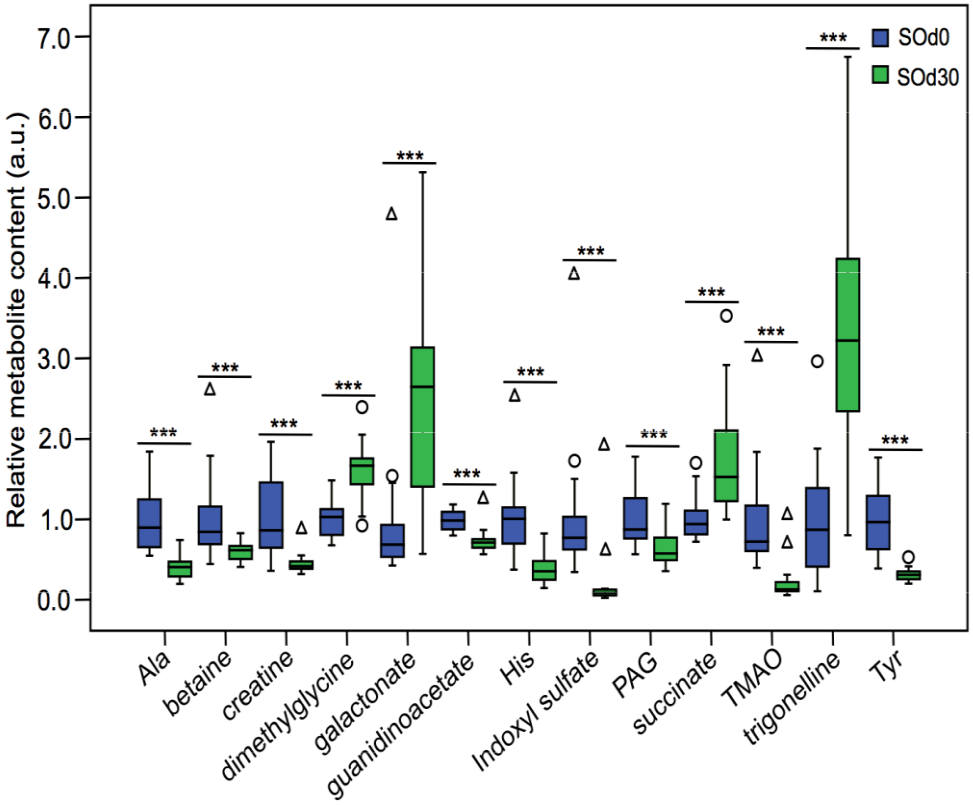


Validated OPLS-DA coefficient plots

Significantly changed urine metabolites during intervention

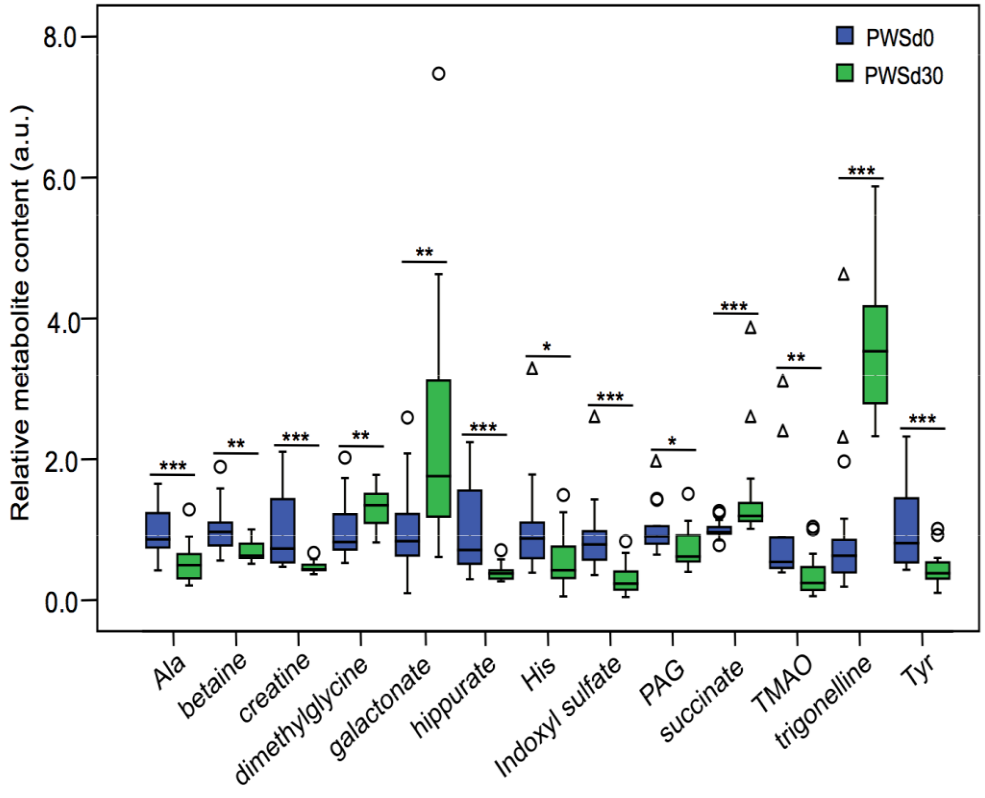
显著变化的关键代谢物

SOd0 *vs* SOd30



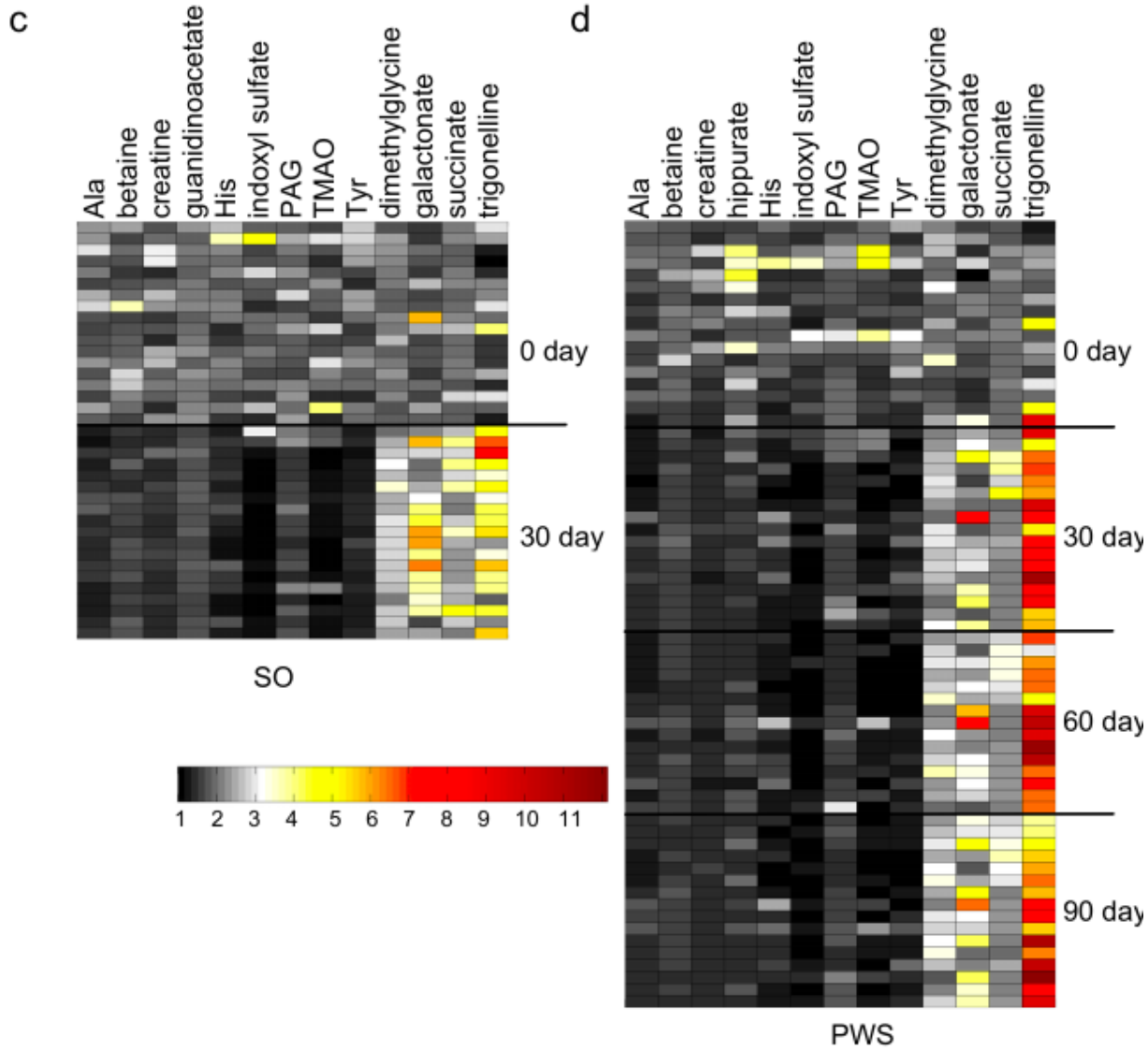
***$P < 0.001$

PWSd0 *vs* PWSd30



*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$

Host-bacteria co-metabolites
细菌与人体共代谢的产物



TMAO

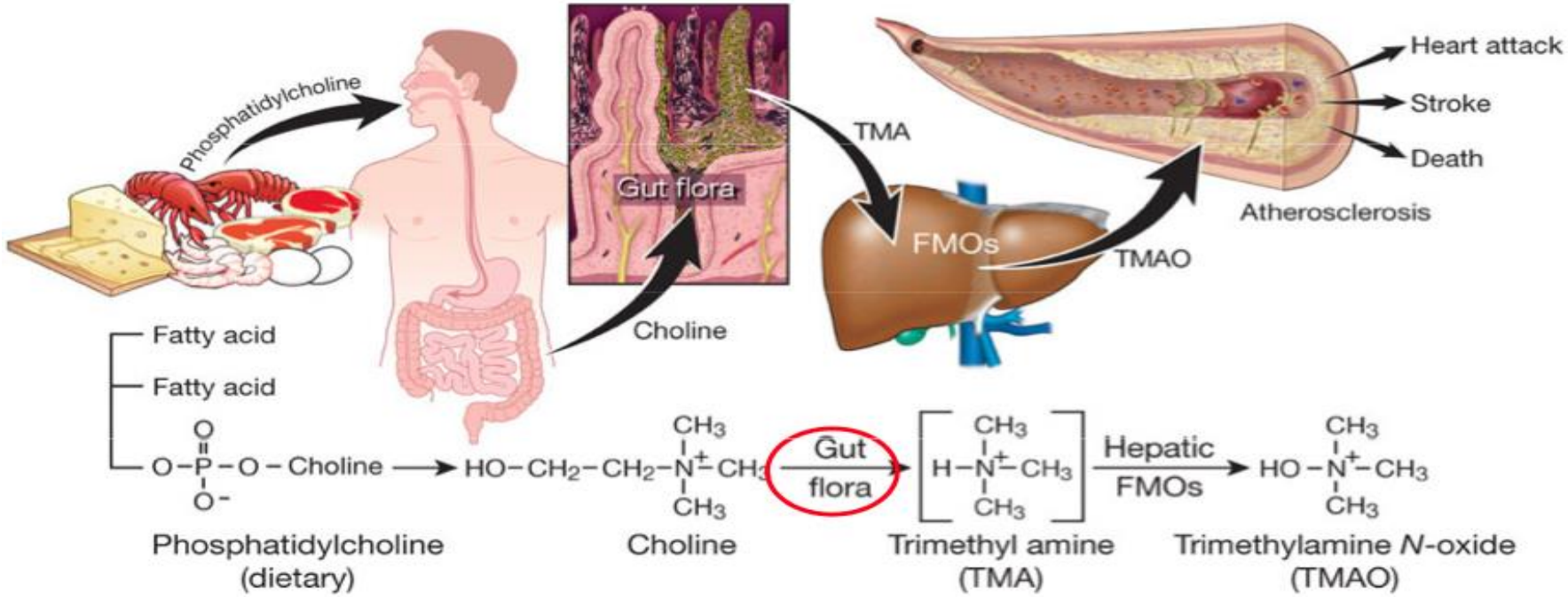
Indoxyl sulfate

PAG

Hippurate

Co-metabolism of choline to TMAO by host liver and gut bacteria
宿主 - 细菌共代谢将胆碱转化为三甲基胺氧化物（TMAO）

TMAO is generated when TMA, produced by bacterial fermentation of dietary fat-derived choline in the gut, enters the bloodstream and is metabolized by the human liver.



Choline TMA-lyase

Choline TMA-lyase-activating enzyme

Wang et al. 2011,Nature

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Metagenomic sequencing
元基因组测序

Groups	Simple Obesity (0 day)	Simple Obesity (30 day)	PWS (0 day)	PWS (30 day)	PWS (60 day)	PWS (90 day)
No. of Samples	21	20	17	17	17	17

Total usable reads per sample

- High-quality reads: 76.0 ± 18.0 million

Total genes

- Non-redundant genes: 2,077,766

Canopy-based algorithm

Identification and assembly of genomes and genetic elements in complex metagenomic samples without using reference genomes

H Bjørn Nielsen[1,2,32], Mathieu Almeida[3–5,32], Agnieszka Sierakowska Juncker[1,2], Simon Rasmussen[1], Junhua Li[6–8],

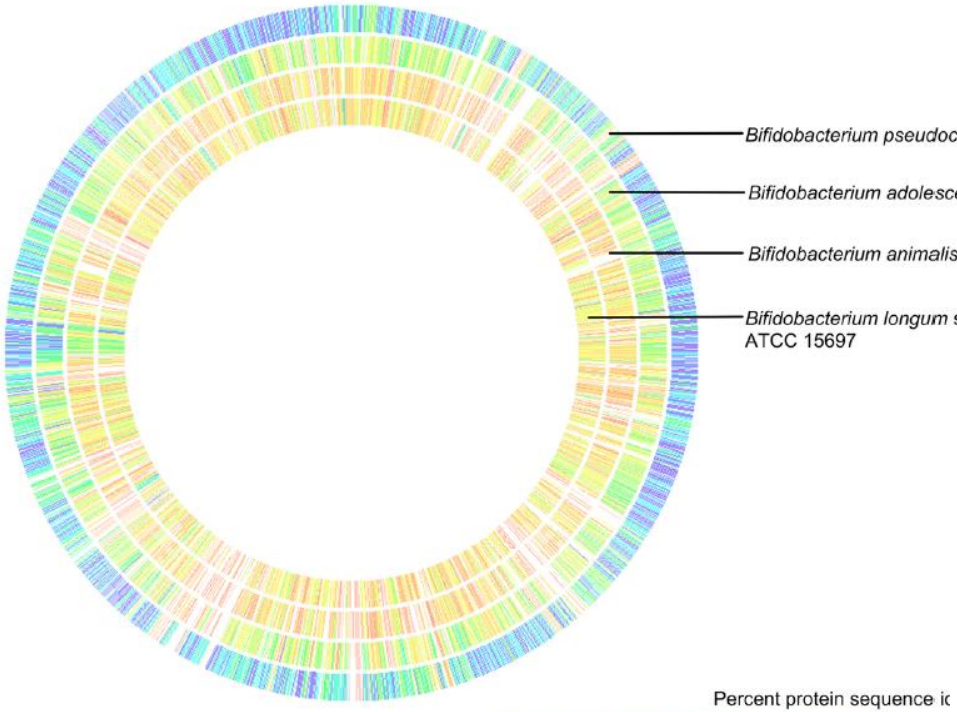
Received 12 February; accepted 22 May; published online 6 July 2014; doi:10.1038/nbt.2939

De Novo assembly of high quality genomes from the metagenomic datasets
基因与基因组的识别

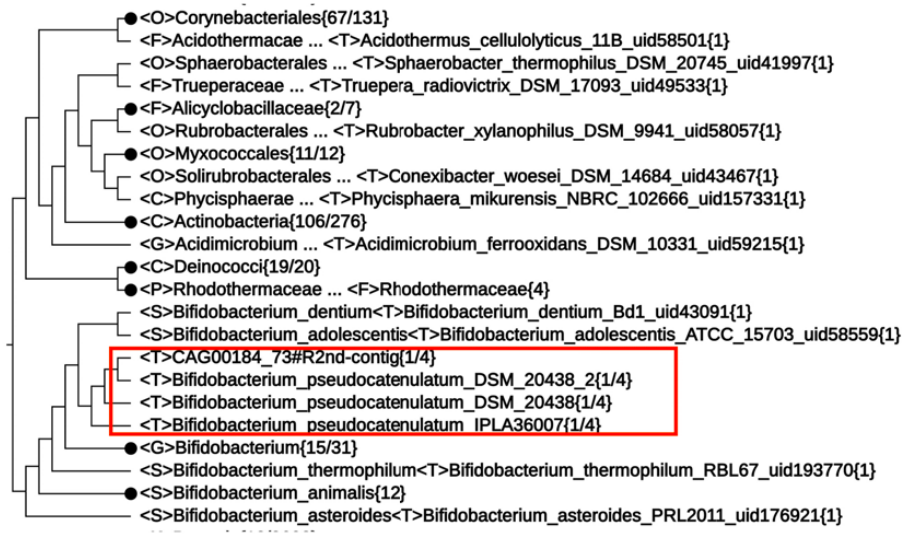
- Canopy-based algorithm
  - Co-abundance gene group (CAG)-genes encoded in the same genetic elements
    - 20,956 (CAGs)
  - CAGs with more than 700 genes are potentially bacterial genomes
    - 376(CAGs)
  - CAGs present in more than 20% of the samples are “prevalent genomes”
    - 161 (CAGs)
  - CAGs with genome assembled
    - 118 high quality draft genomes
    - 5 of 6 criteria of the HMP reference genomes

High quality draft genome assembled from the metagenomic datasets

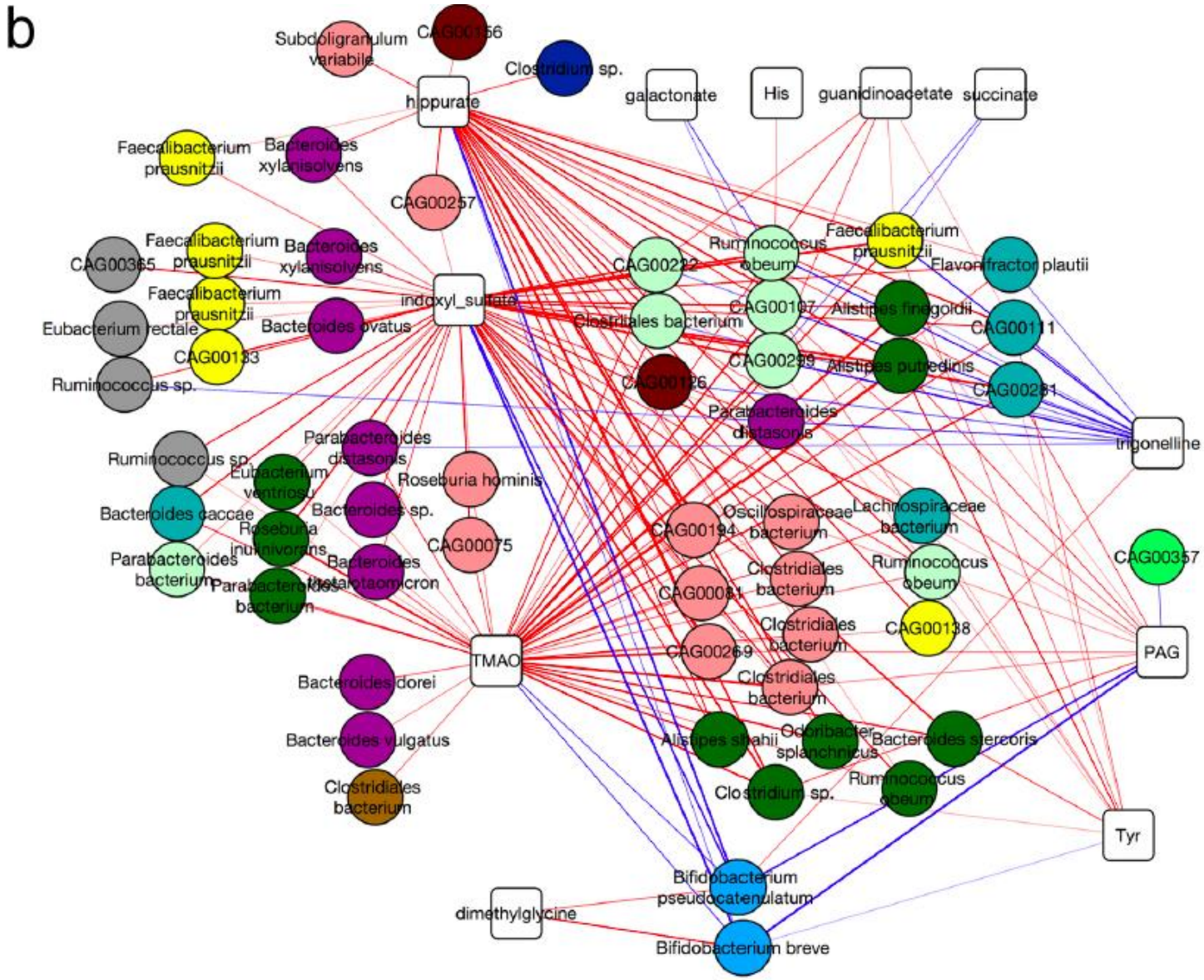
A



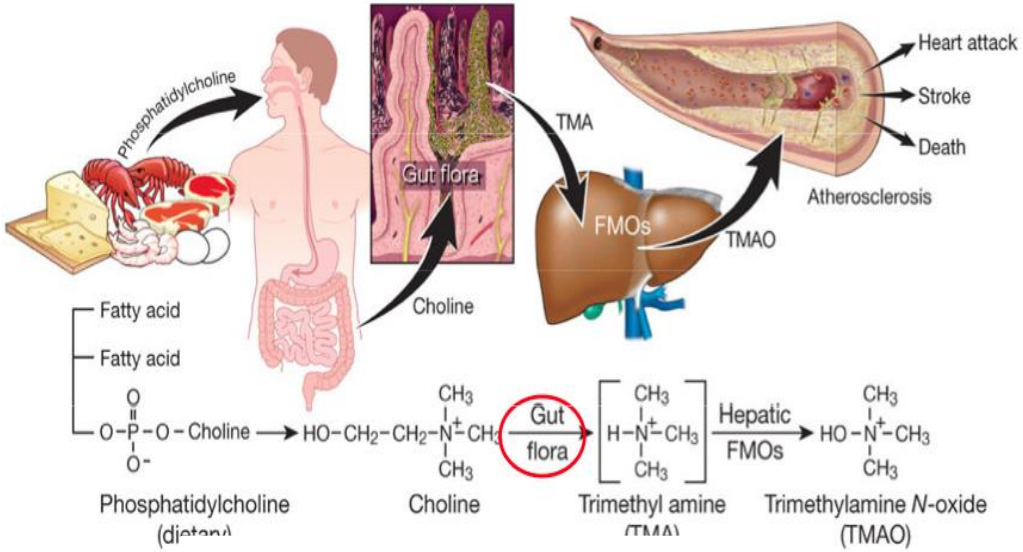
B



Correlation between CAGs and key urine metabolites
细菌基因组与尿液代谢物的相关



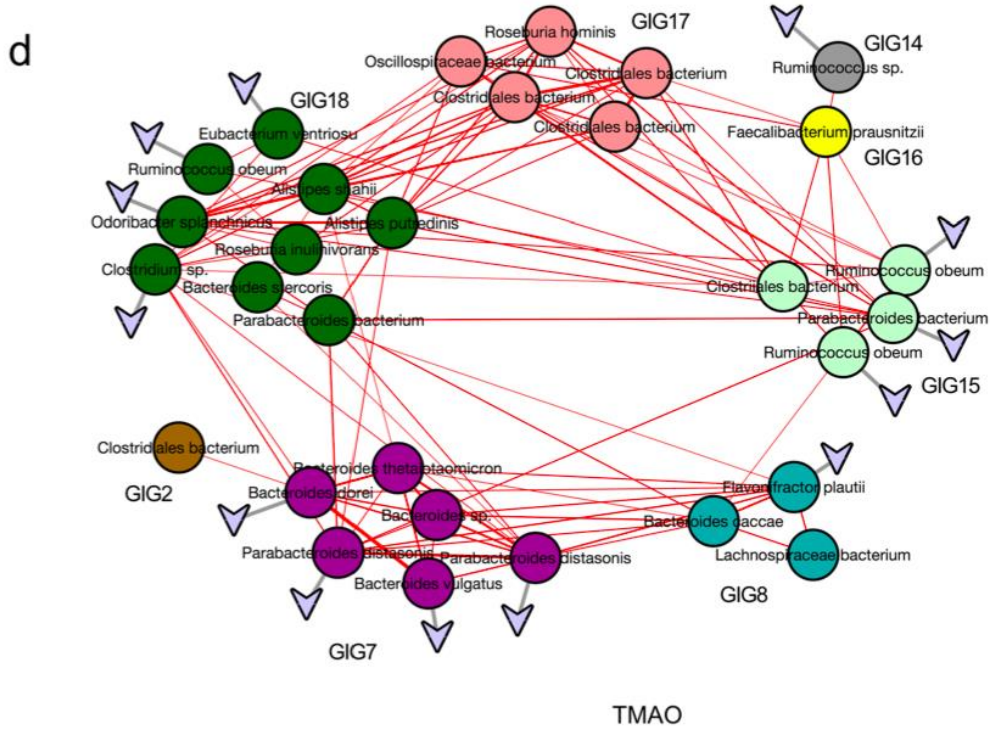
Bacterial genomes encoding TMA-producing genes
携带编码TMA产生酶基因的细菌基因组



Choline TMA-lyase

Choline TMA-lyase-activating enzyme

Wang et al. 2011,Nature

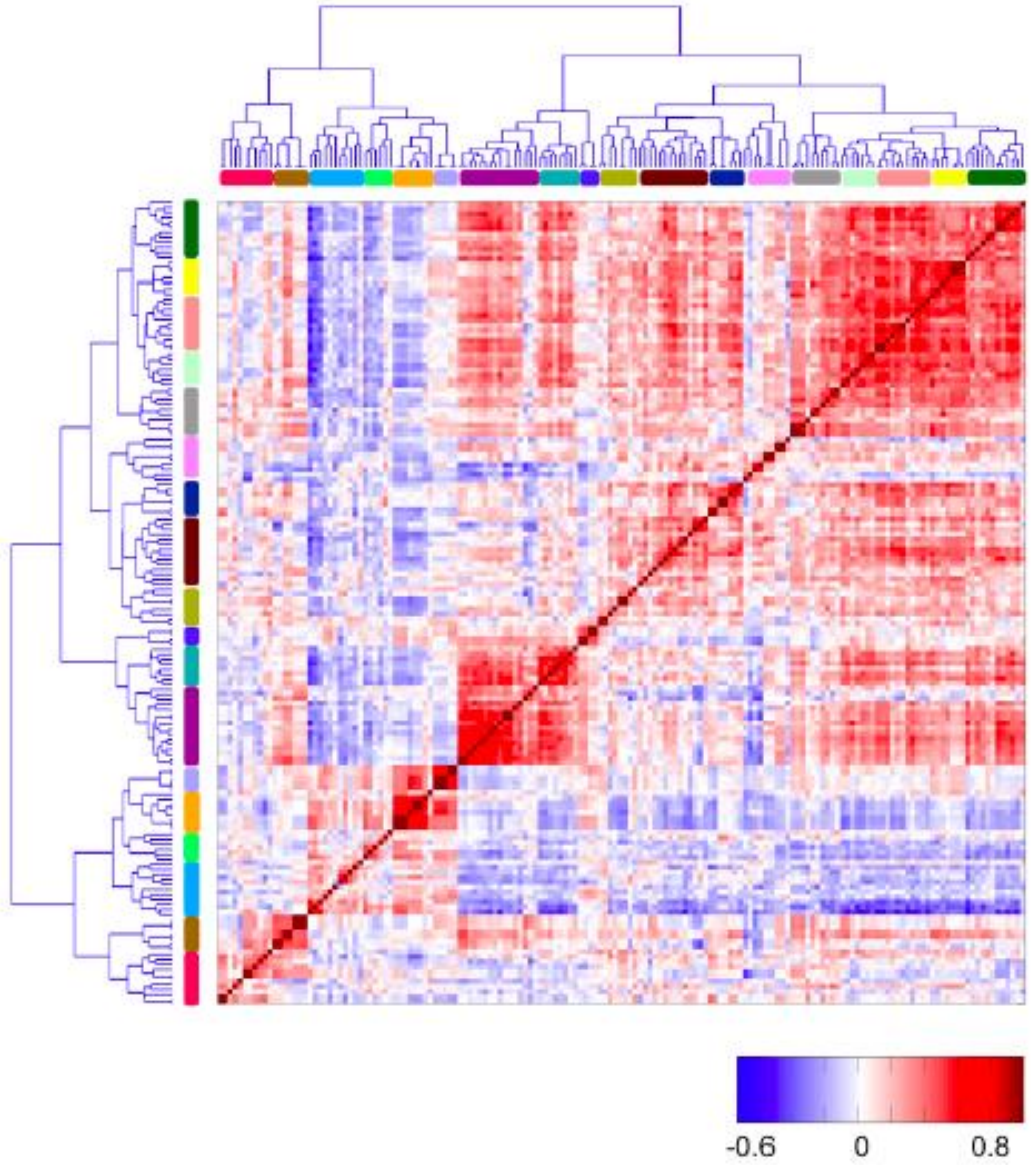


TMAO is generated, when TMA, produced by bacterial fermentation of dietary fat-derived choline in the gut, enters the bloodstream and is metabolized by the human liver.

31/118 CAGs have positive association with urine TMAO
14/31 CAGs have both TMA-lyase and its activating enzyme genes

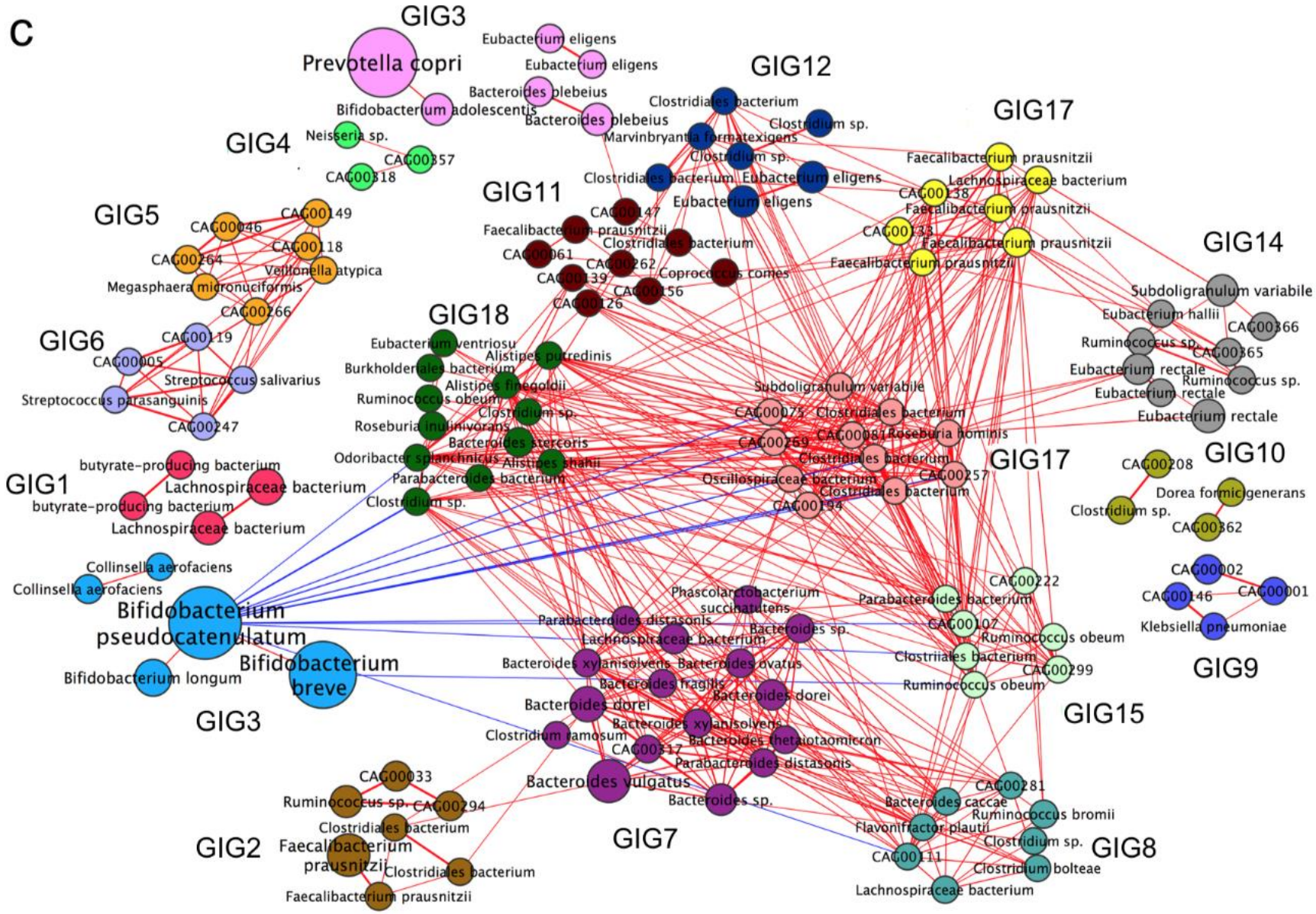
Delineating genome interaction groups (GIGs)
基因组互作群

161 CAGs
Populations

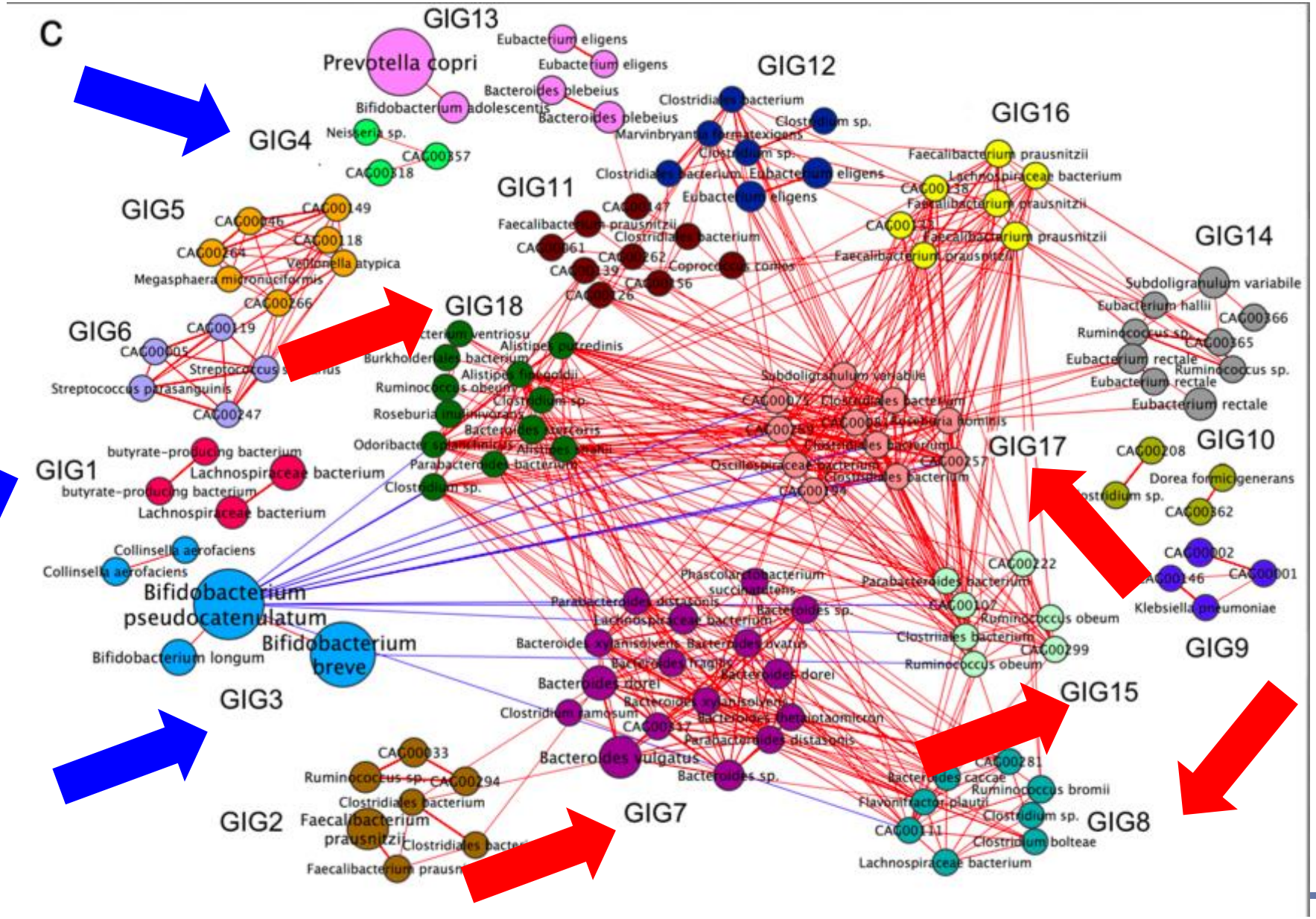


18 GIGs
Guilds

Co-occurrence network analysis to define Genome Interaction Groups (GIGs) 基因组互作网络

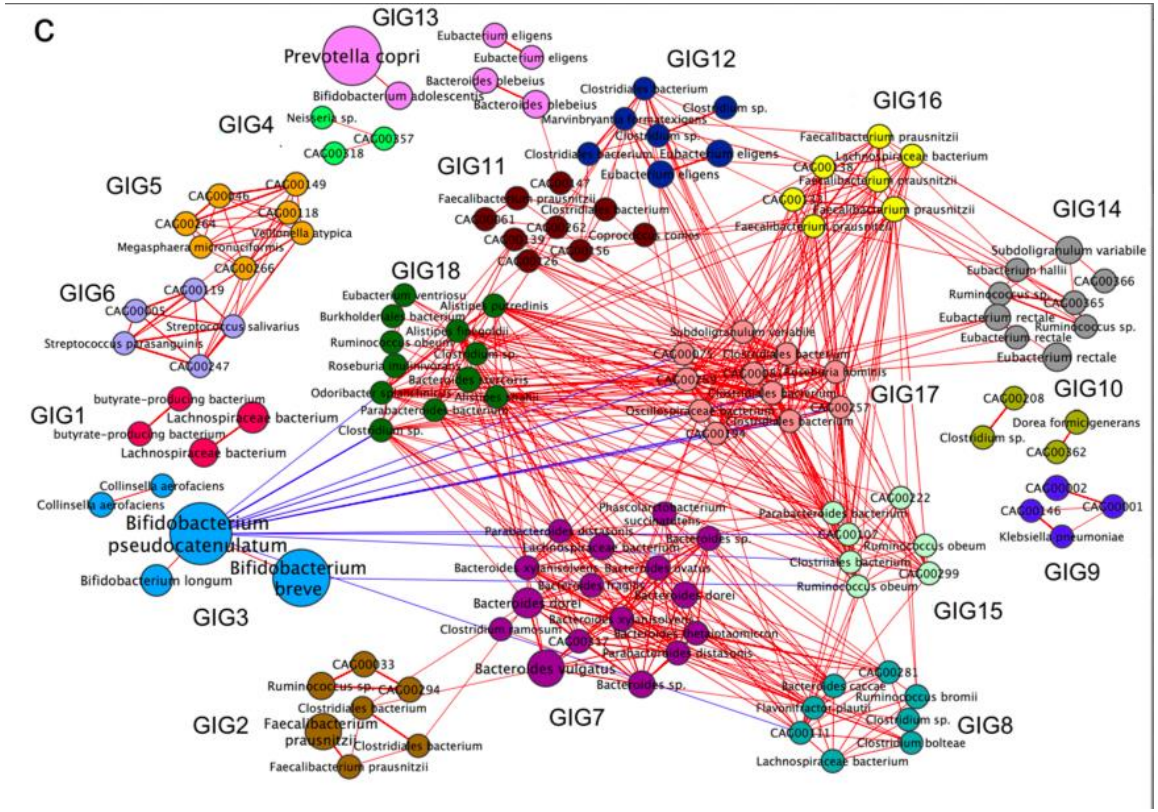


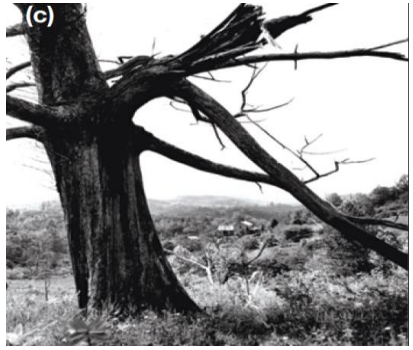
Correlation between GIGs and disease phenotypes



Foundation species and functional groups (guilds) of bacterial populations in the gut ecosystem

Healthy





Diseased

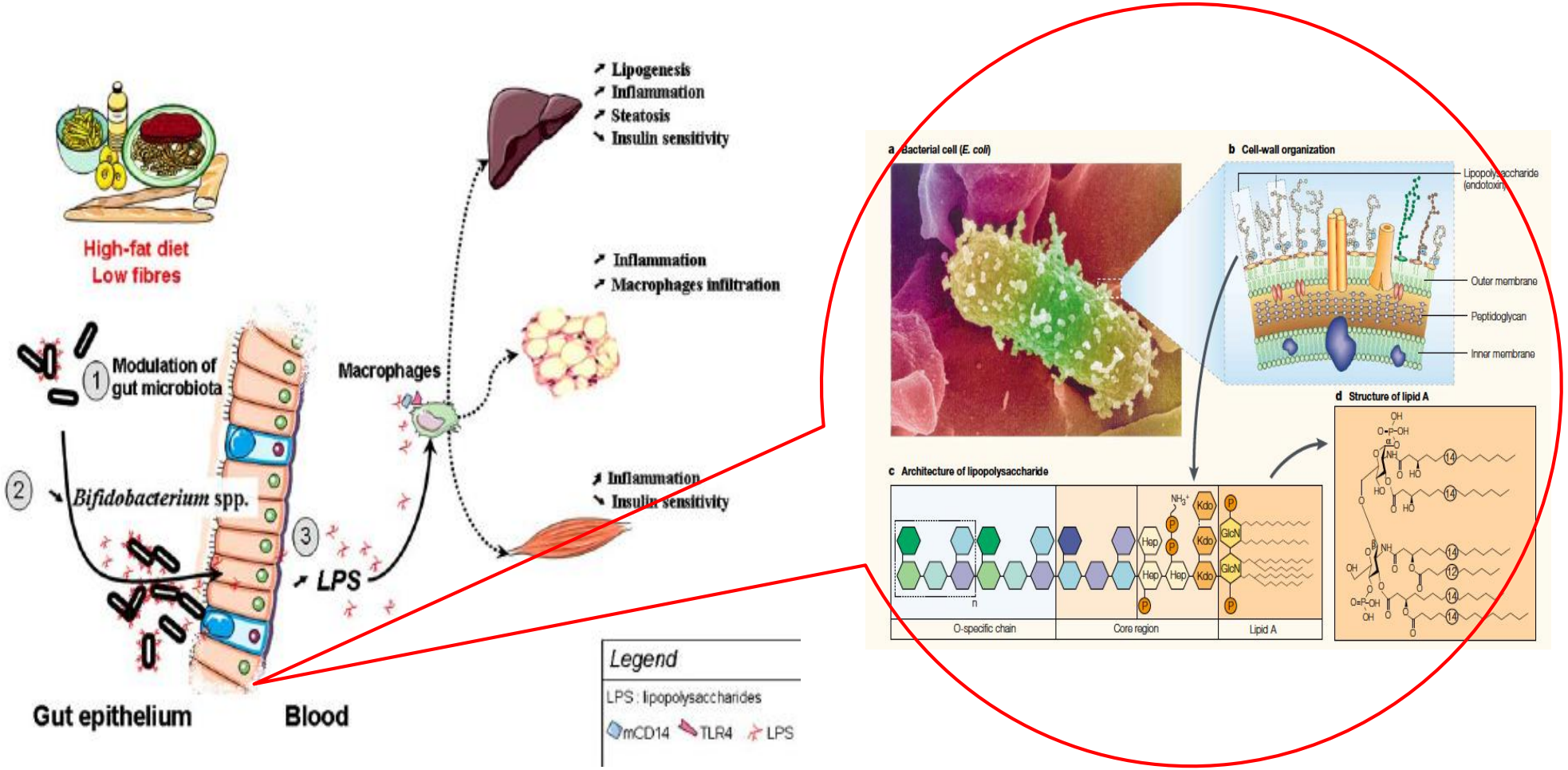
REVIEWS REVIEWS REVIEWS

Loss of foundation species: consequences for the structure and dynamics of forested ecosystems

Aaron M Ellison[1*], Michael S Bank[1], Barton D Clinton[2], Elizabeth A Colburn[1], Katherine Elliott[2],

LPS endotoxin from gut microbiota can induce obesity

肠道菌群产生的内毒素可以引起肥胖



P.Cani, 2007

Dietary modulation of gut microbiota for obesity control
以肠道菌群为靶点的肥胖症营养干预

Weight **174.9** kg

BMI **58.8**

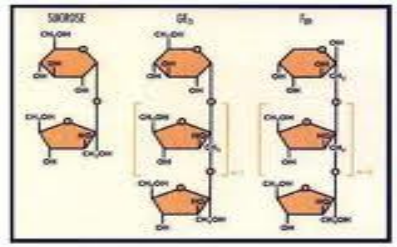
Lost 51.4kg
over 23 weeks

Dietary intervention
23 weeks

WTP Diet

Weight **123.5** kg

BMI **41.5**



Whole grains, Traditional Chinese medicine food and Prebiotics (WTP diet)

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Recovery of metabolic health over time
代谢健康的恢复

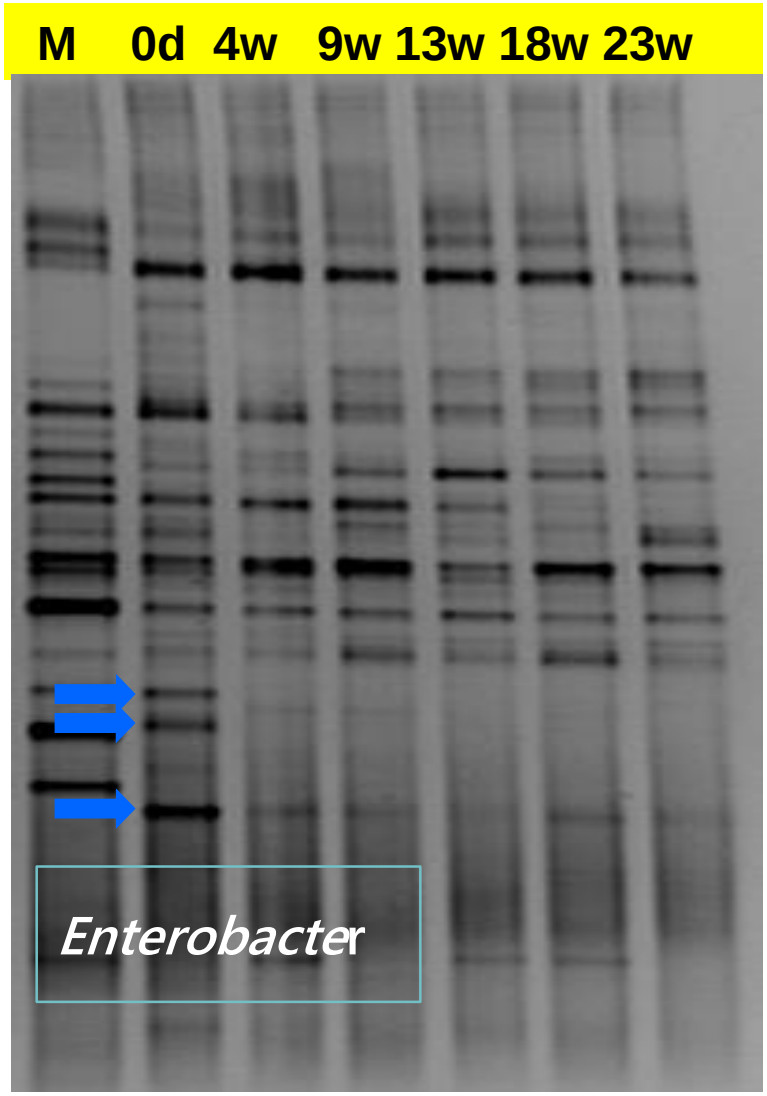
Parameter	Baseline	9 week	23 week	Medical reference range
Body weight (kg)	174.9	144.8	123.5	/
Body weight loss (kg)	0	30.1	51.4	/
Fasting Glycaemia (mmol/L)	8.95	4.76	5.4	3.6-6.1
Fasting Insulinemia (μIU/mL)	58.7	25.8	23.0	3.0-25
Blood pressure (mmHg)	100/150	80/120	75/120	80/120
Total cholesterol (mmol/l)	5.53	4.44	4.78	3-5.17
Triglycerides (mmol/l)	2.68	1.72	1.18	0-1.7
Aspartate aminotransferase (U/L)	122	51	31	10-47
C-reactive protein (mg/L)	14.1	9.4	9.51	0-10
IL-6 (pg/mL)	6.56	4.39	2.72	/
Adiponectin (ng/mL)	1839.41	1925.63	4145.38	/
LBP (μg/mL)	8.13	2.44	5.76	/

Inflammation

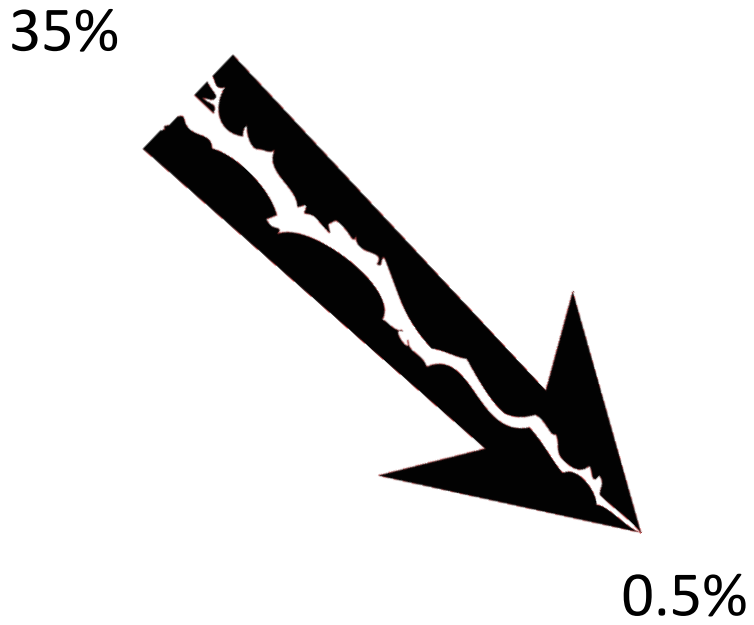
Endotoxin load

HbA1C 糖化血红蛋白：7.58%→5.44%→4.52%(3.8-5.8%)

Decline of endotoxin-producing populations
条件致病菌的下降



Reduction of the pathogenic population



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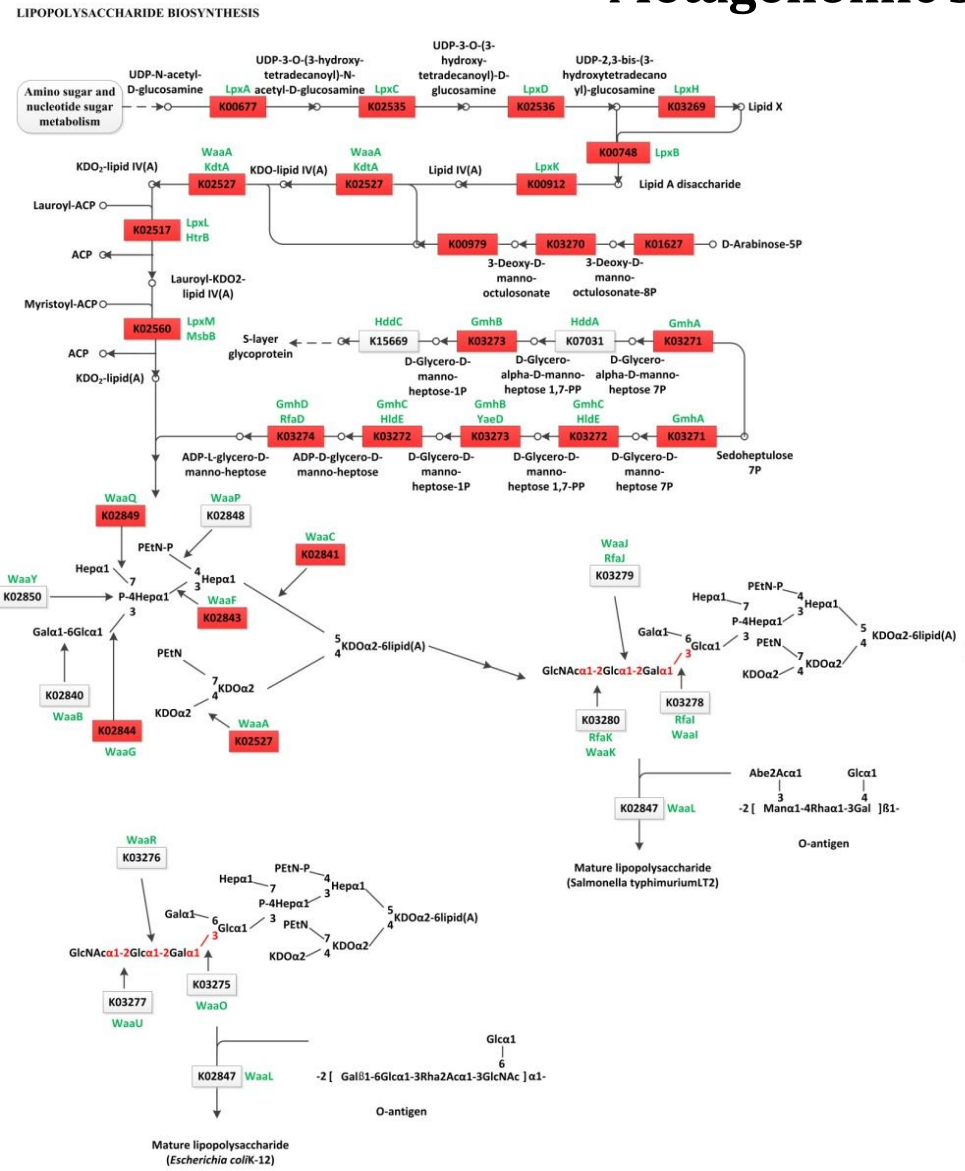
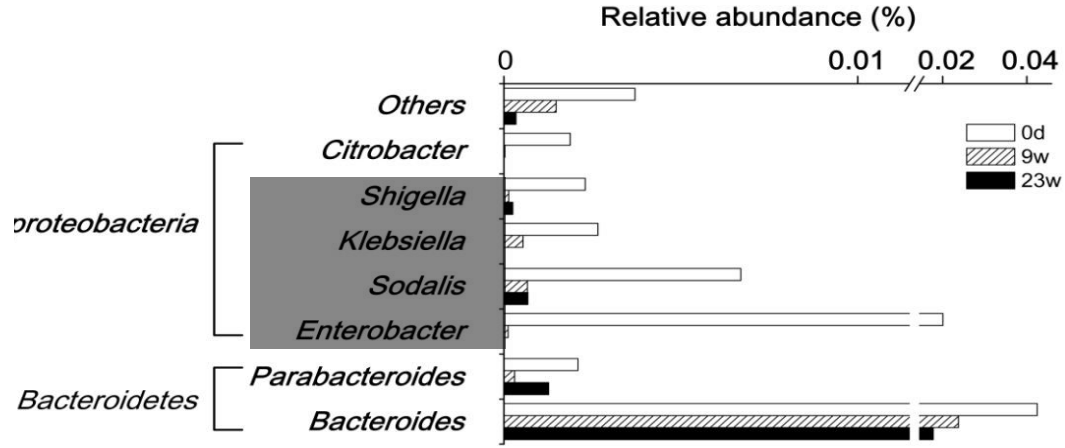
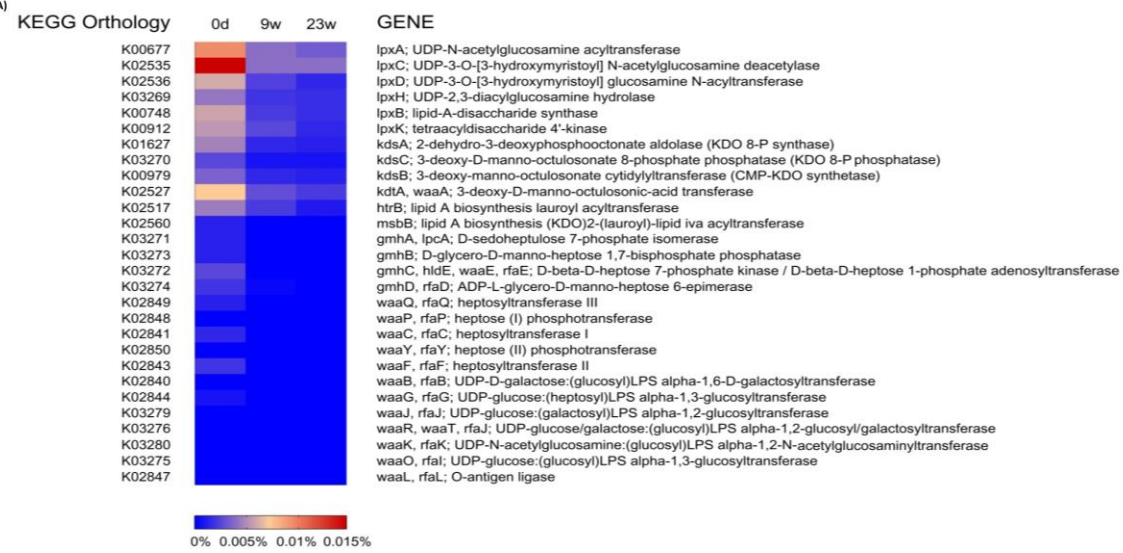
Reduction of genes of LPS synthetic pathway
内毒素合成基因丰度的下降

Metagenomic sequencing analysis at 0, 9 and 23 weeks







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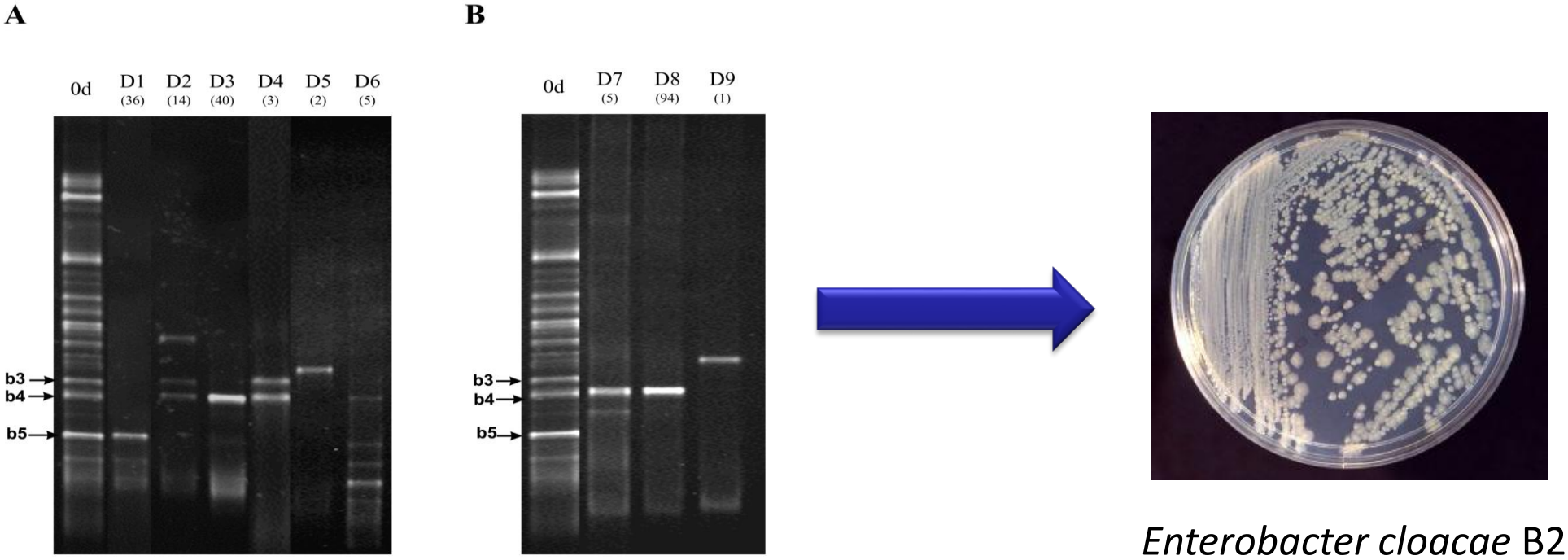
Sequence-guided isolation of the putative agent
序列引导下的菌种分离

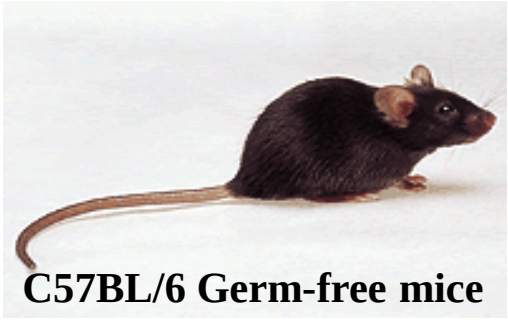


Enterobacter cloacae B29

Disease reproduction in germfree mice

在无菌动物中复制疾病

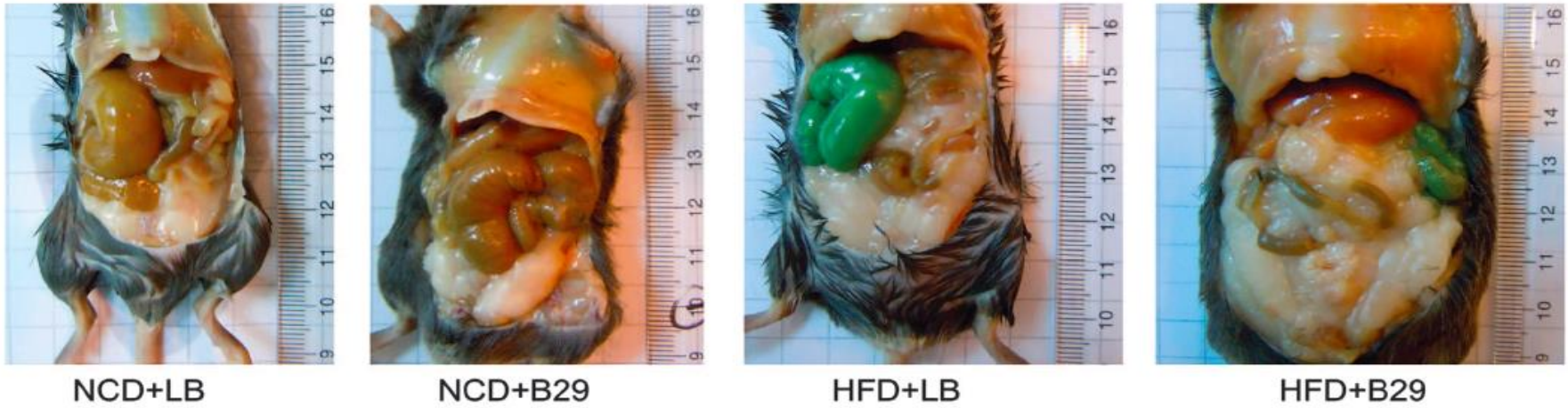
Gnotobiotic model of obesity

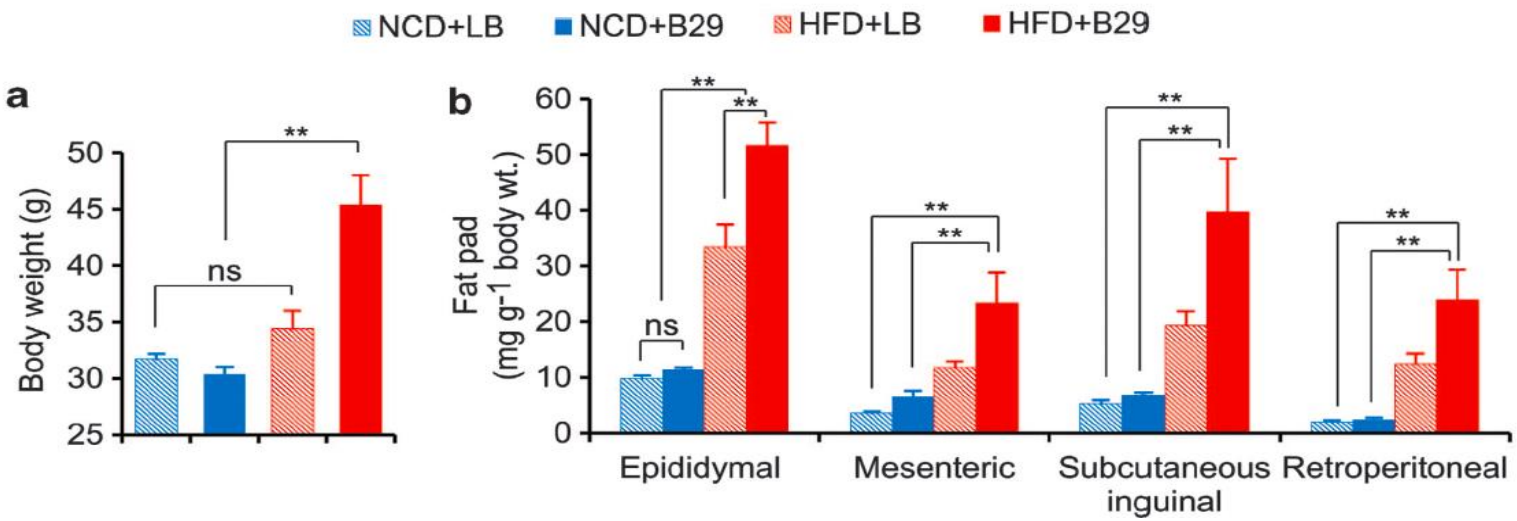


C57BL/6 Germ-free mice

Normal chow & Germ-free	Normal chow & B29	High fat diet & Germ-free	High fat diet & B29	High fat diet & *Bifidobacterium* sp.

Disease reproduction in germfree mice
B29引起动物肥胖





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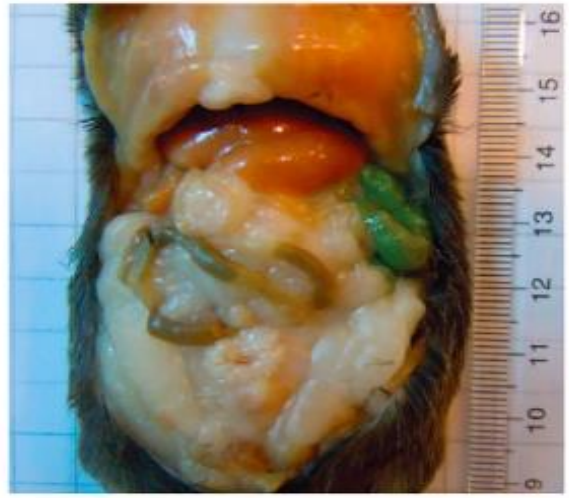
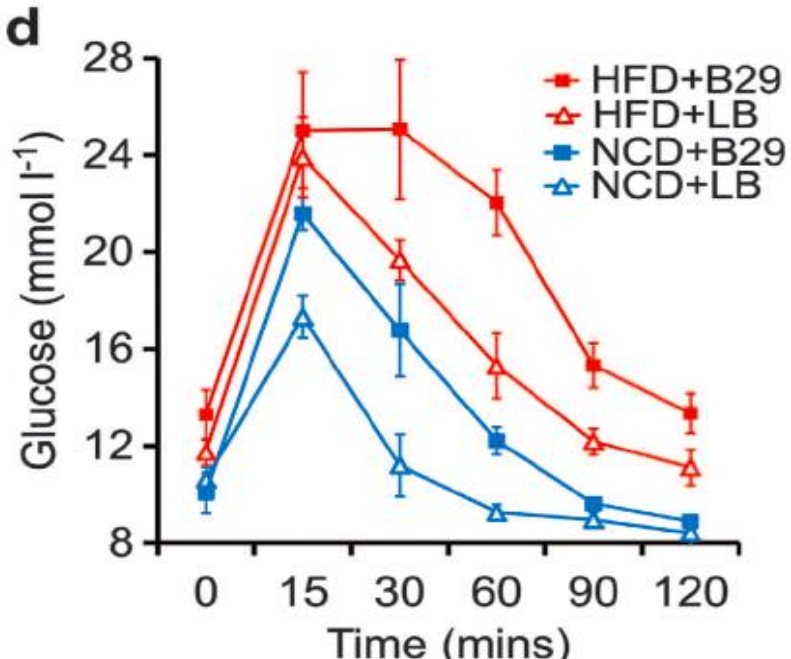
Disease reproduction in germfree mice
B29引起动物肥胖

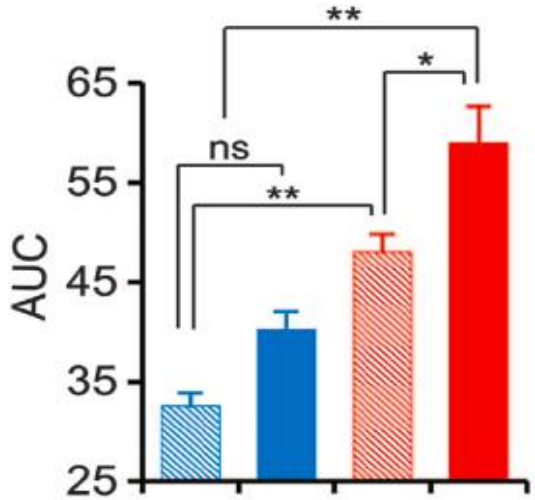

NCD+LB

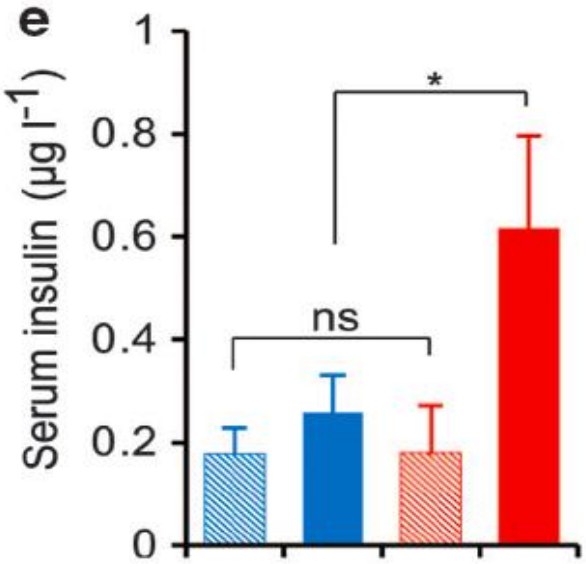

NCD+B29


HFD+LB


HFD+B29

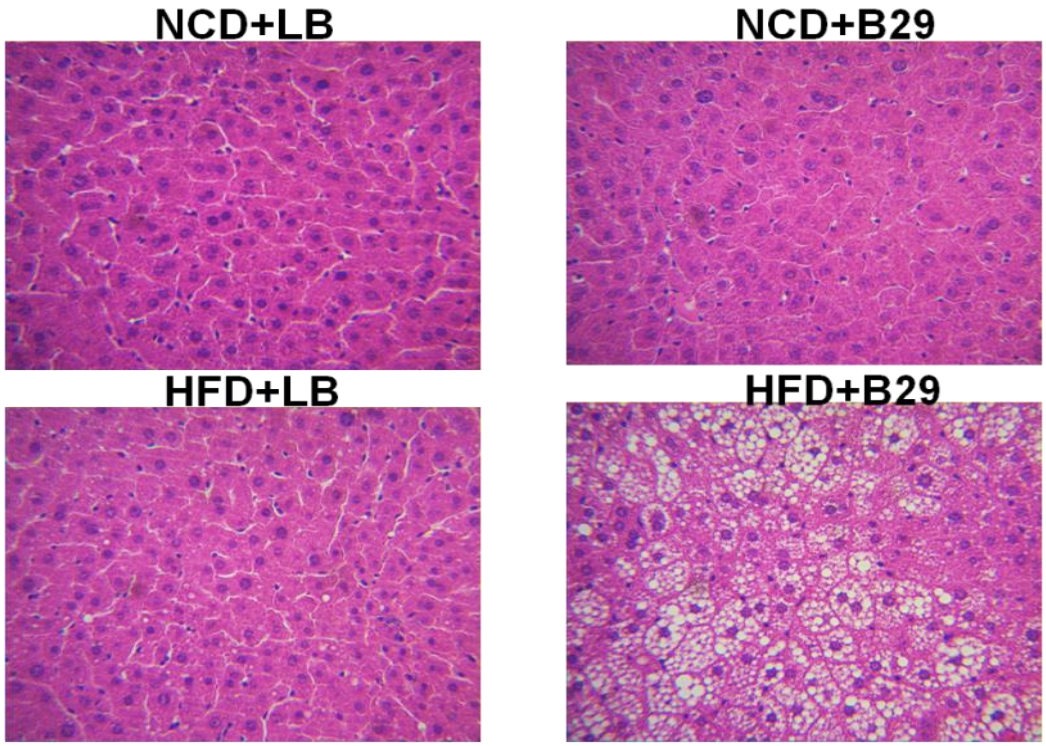




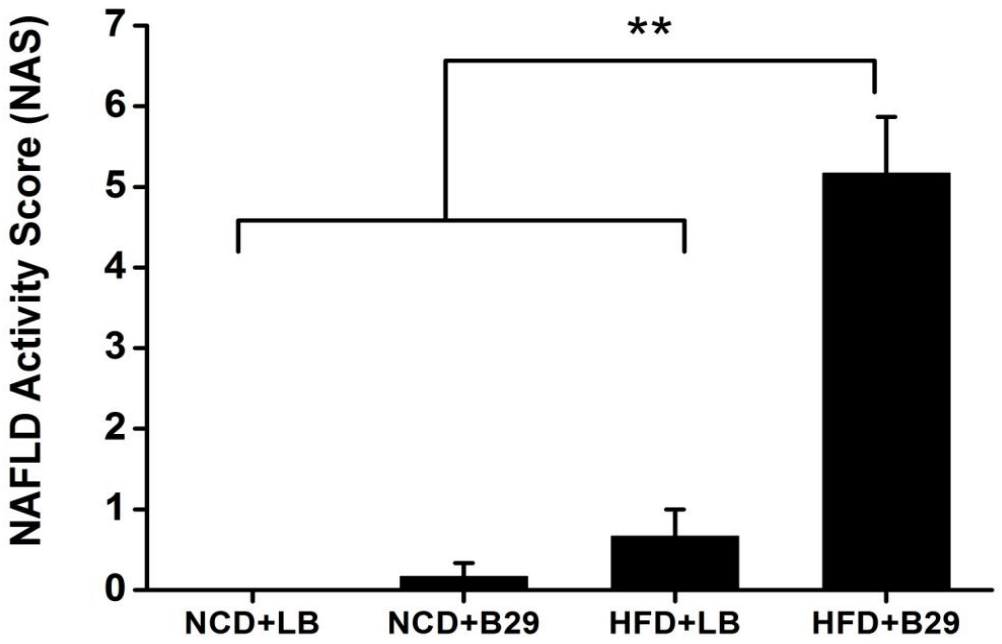


Disease reproduction in germfree mice
B29引起动物肥胖

A. HE

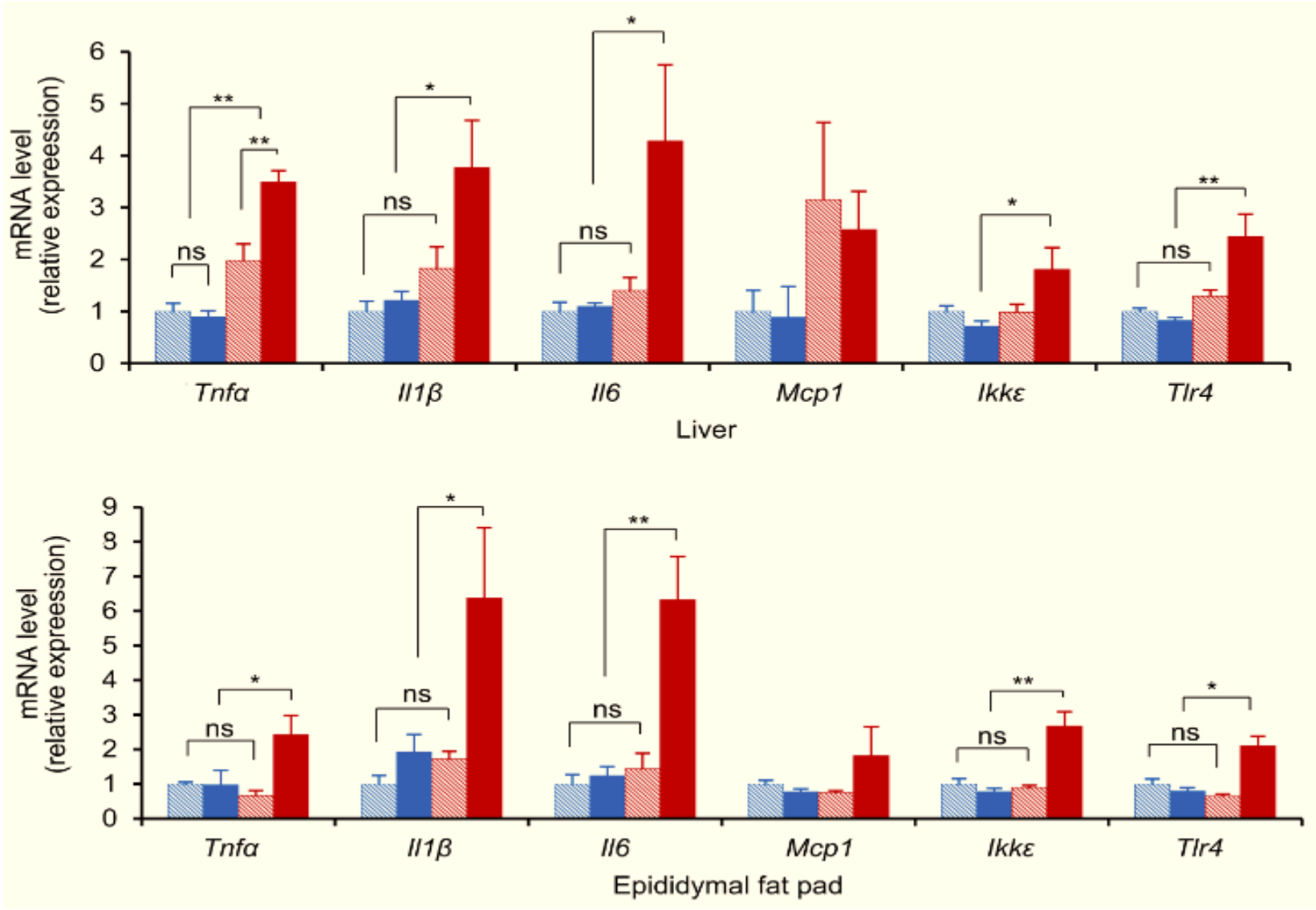


B. NAFLD Activity Score

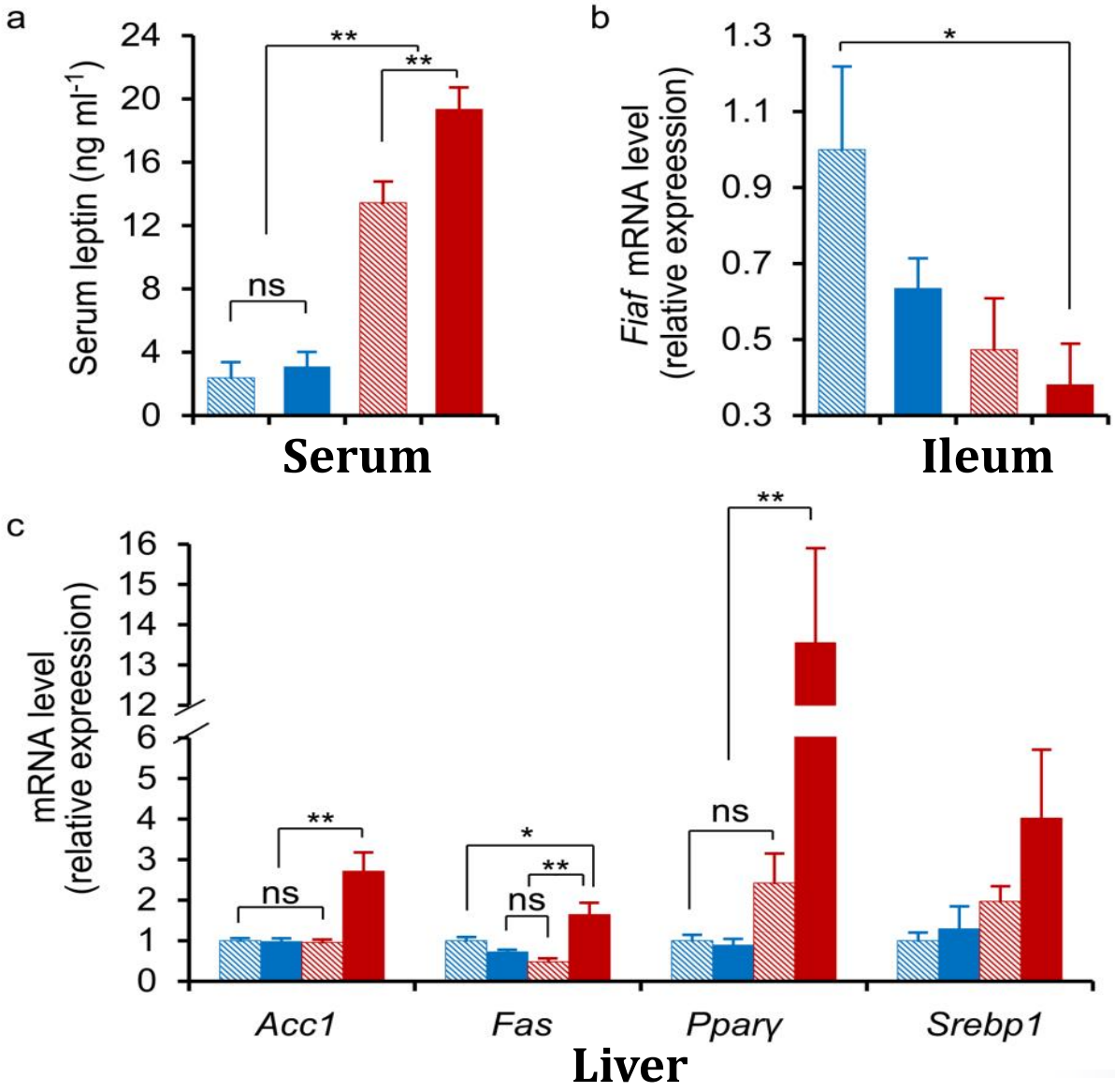


B29 induced NAFLD

Local inflammation in liver and fat pad
脂肪垫和肝脏有炎症



Disrupted lipometabolism
脂代谢基因表达被扰乱



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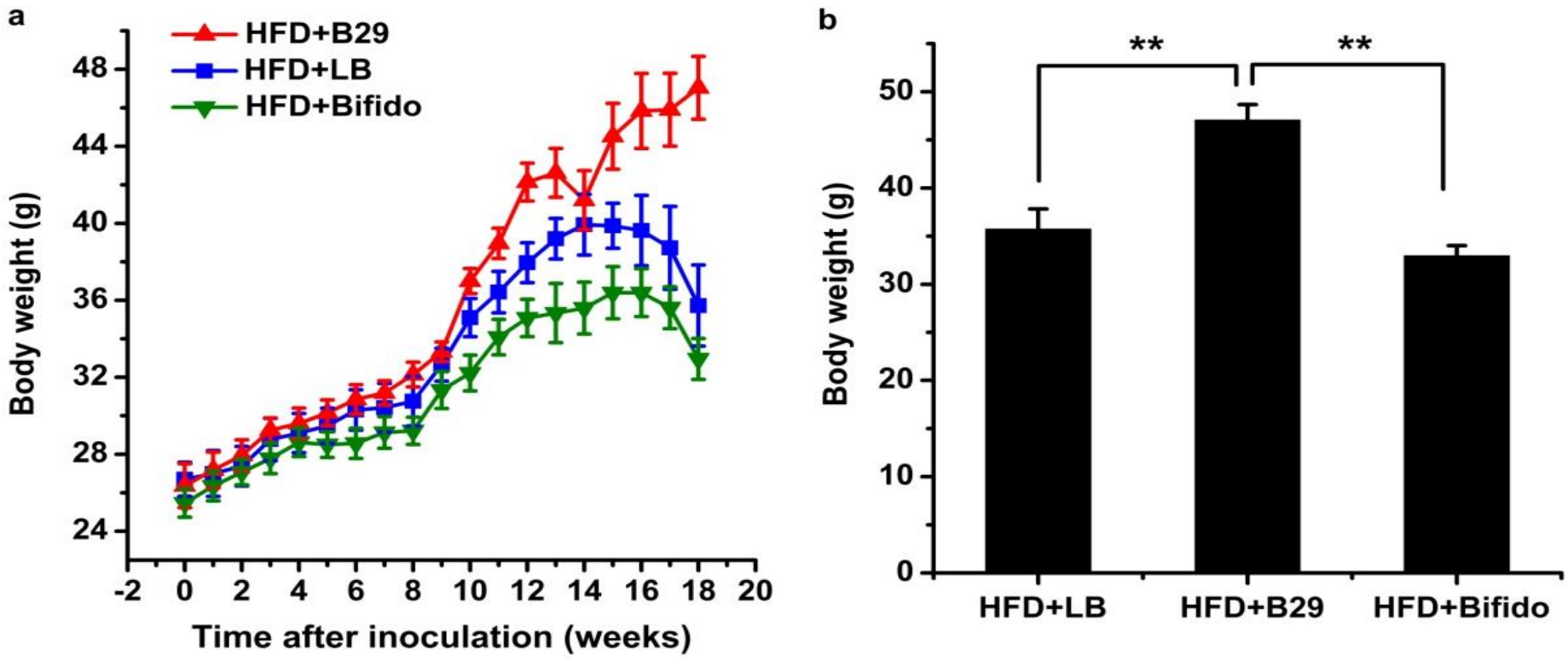
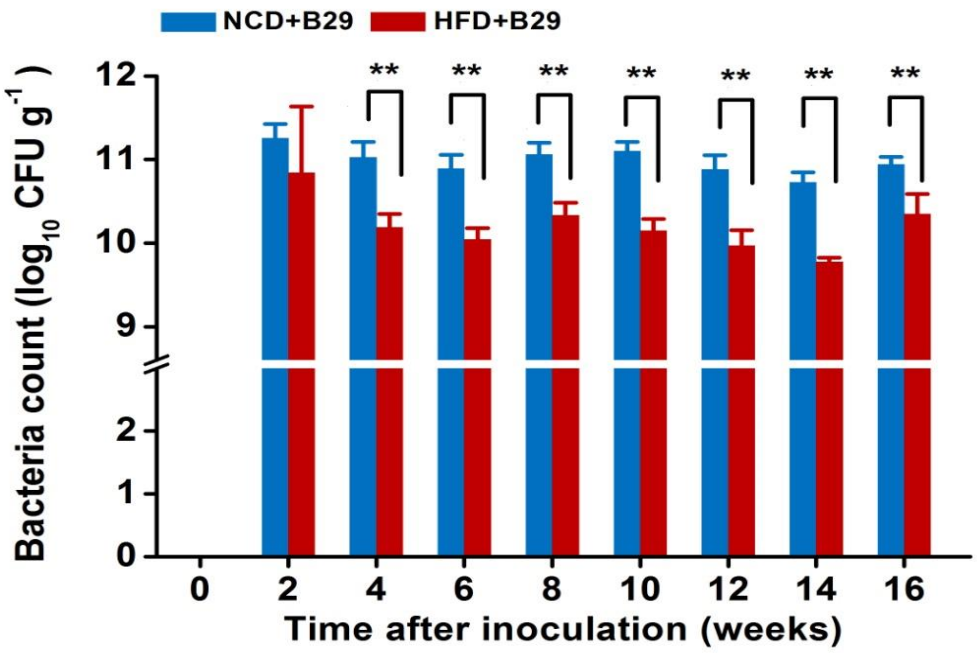
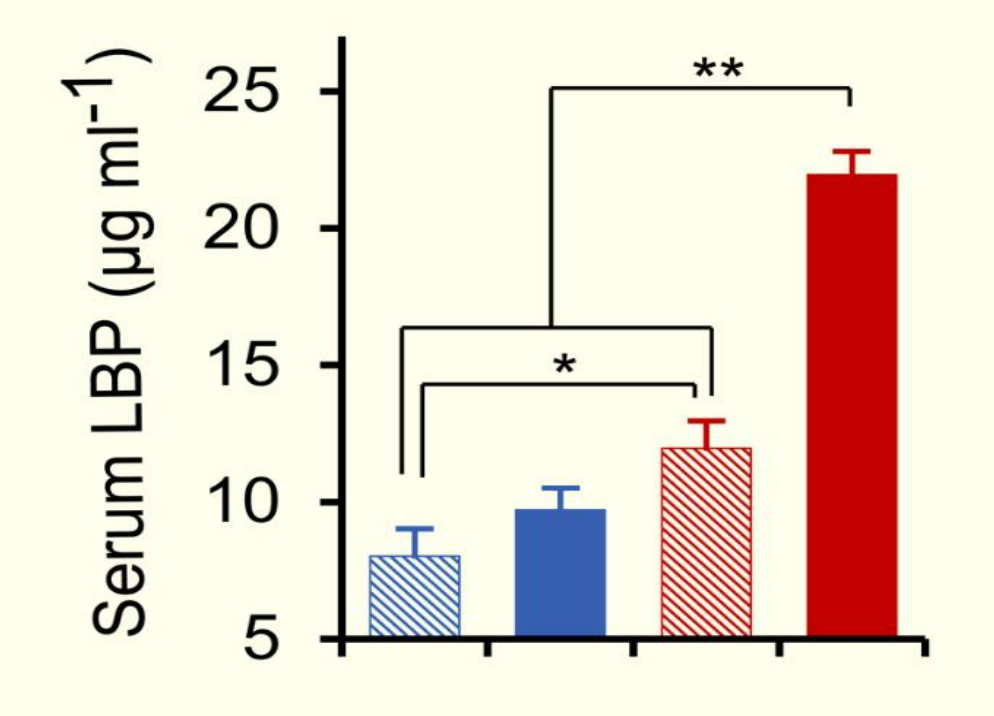
Its not "Any" bacteria
病菌增加体重，有益菌可以减体重



Bifidobacterium sp. **did not promote obesity when mono-associated with germfree mice under high fat feeding**

Endotoxin from the gut under B29 with high fat feeding
B29产生的内毒素在高脂饲料组入血





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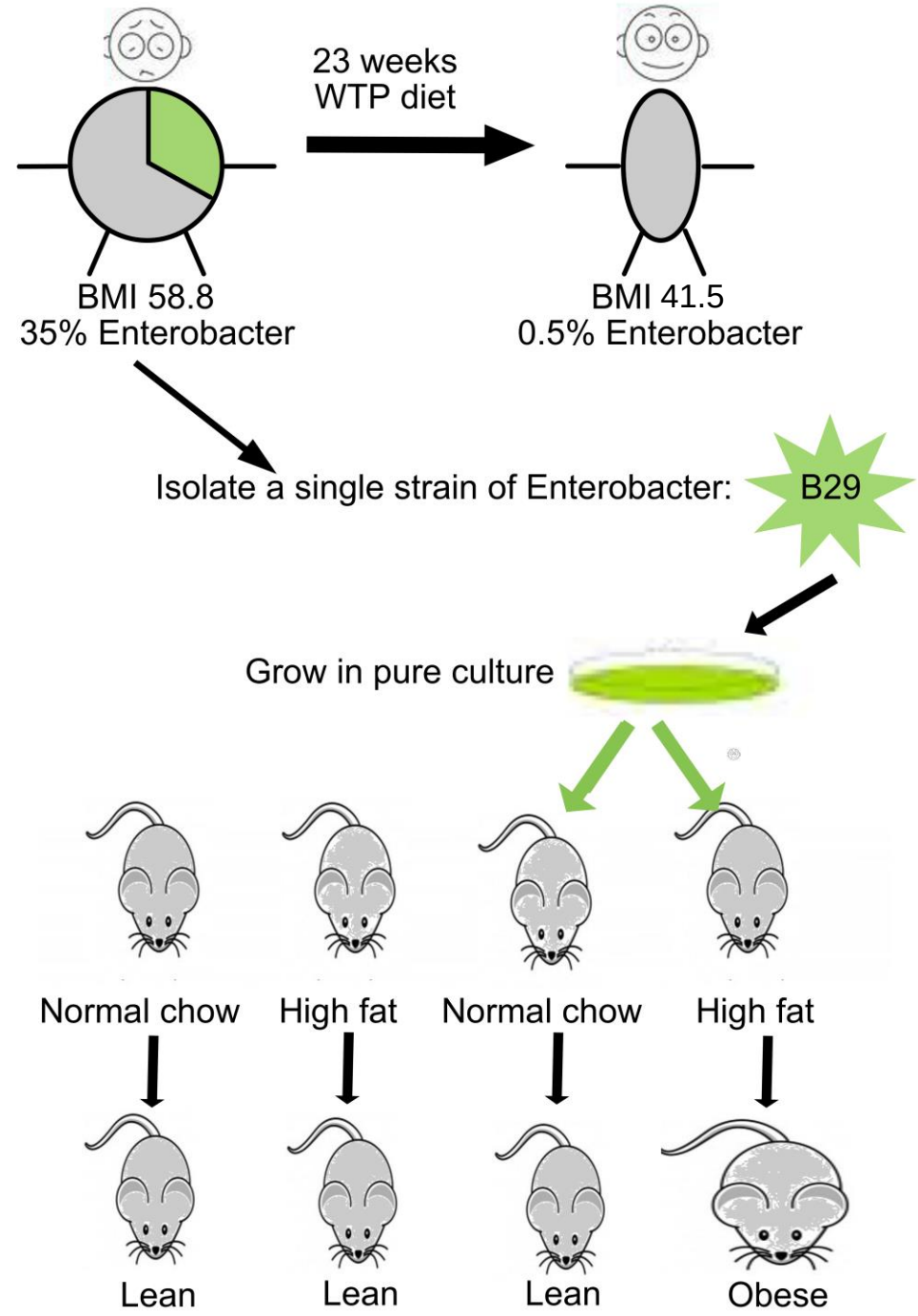
SHORT COMMUNICATION

An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice

Na Fei[1] and Liping Zhao[1,2]
[1]State Key Laboratory of Microbial Metabolism and School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai, China and [2]Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China

Lipopolysaccharide endotoxin is the only known bacterial product which, when subcutaneously infused into mice in its purified form, can induce obesity and insulin resistance via an inflammation-mediated pathway. Here we show that one endotoxin-producing bacterium isolated from a morbidly obese human's gut induced obesity and insulin resistance in germfree mice. The endotoxin-producing *Enterobacter* decreased in relative abundance from 35% of the volunteer's gut bacteria to non-detectable, during which time the volunteer lost 51.4 kg of 174.8 kg initial weight and recovered from hyperglycemia and hypertension after 23 weeks on a diet of whole grains, traditional Chinese medicinal foods and prebiotics. A decreased abundance of endotoxin biosynthetic genes in the

One endotoxin-producing opportunistic pathogen isolated from an obese human gut caused obesity when mono-associated with germfree mice.



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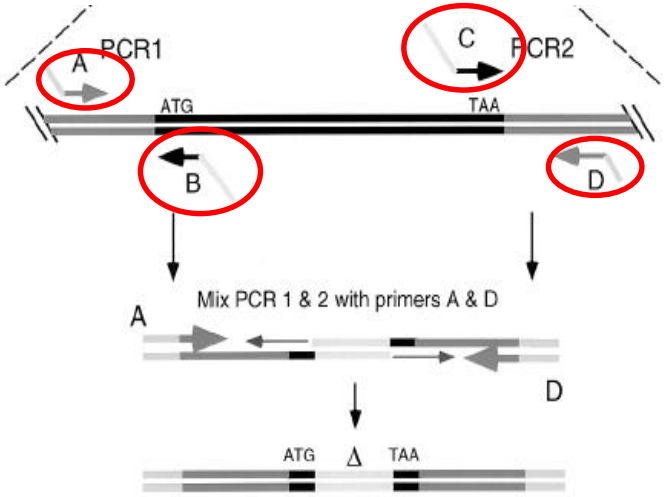
Is LPS endotoxin the major factor for B29 to induce obesity?

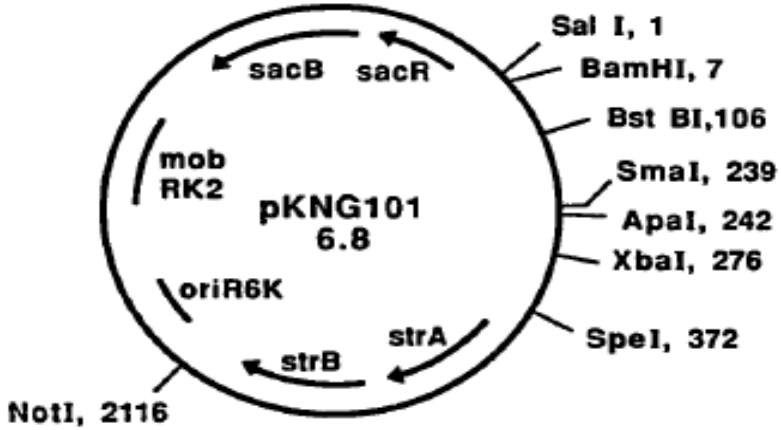
Unpublished study in collaboration with INRA

Suicide vector strategy for B29-lps-mutant Strain

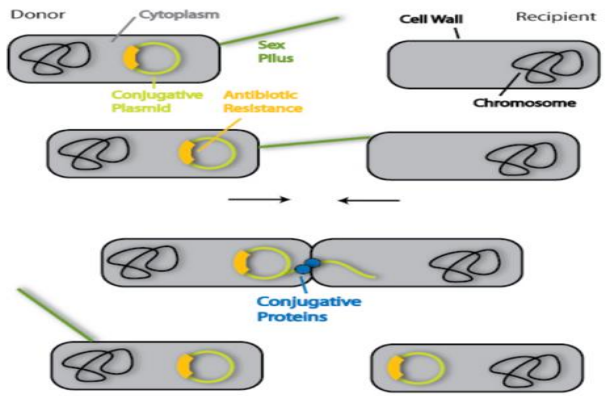
1. SOE PCR:splicing by overlap extension



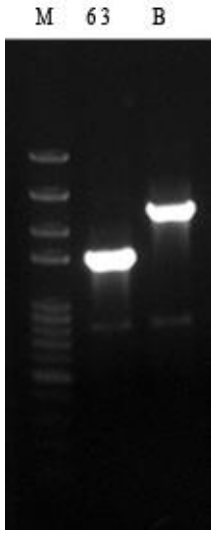
2. Constructing recombinated Plasmid PKNG101



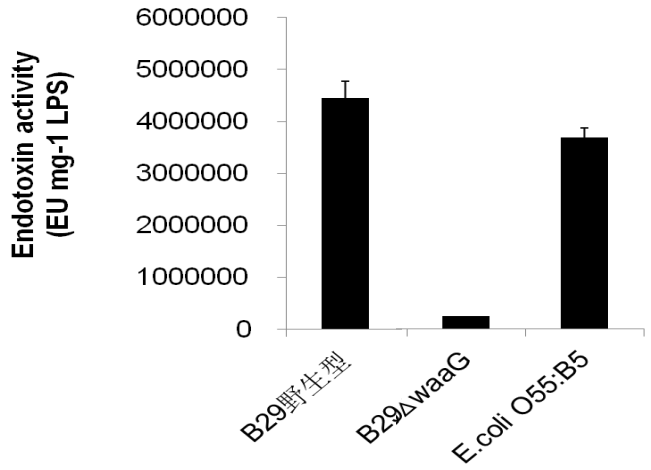
3. Bacterial Conjugation



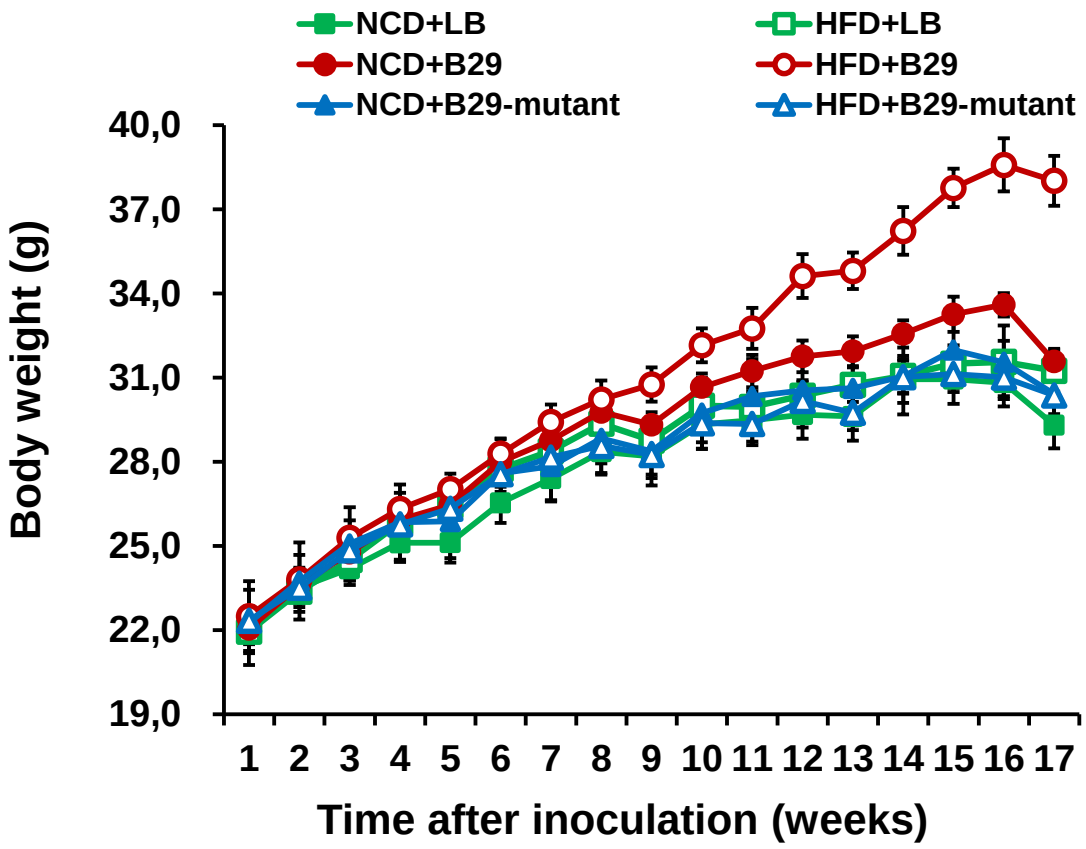
4. Single crossover and Double crossover recombination in B29

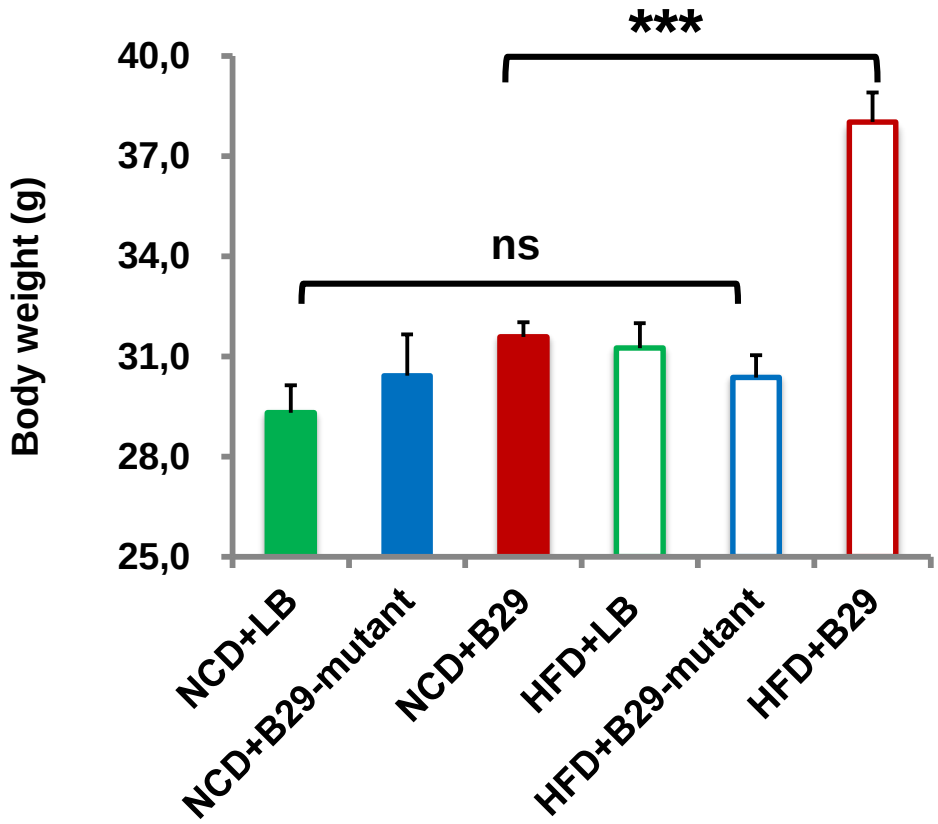


limulus amebocyte lysate test

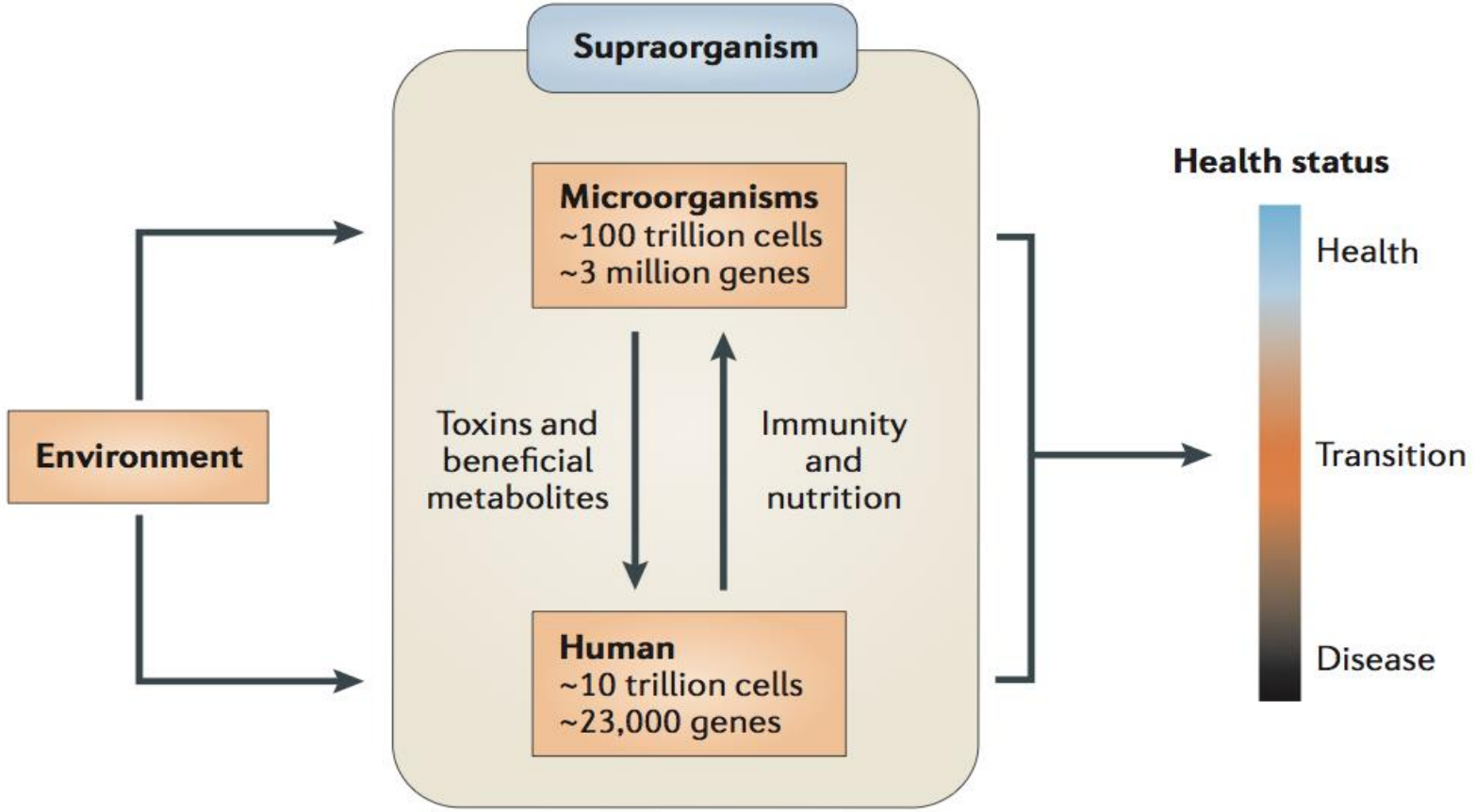


The *E. cloacae* B29 LPS-mutation lost the capacity to induce the germfree mice obesity under HFD feeding





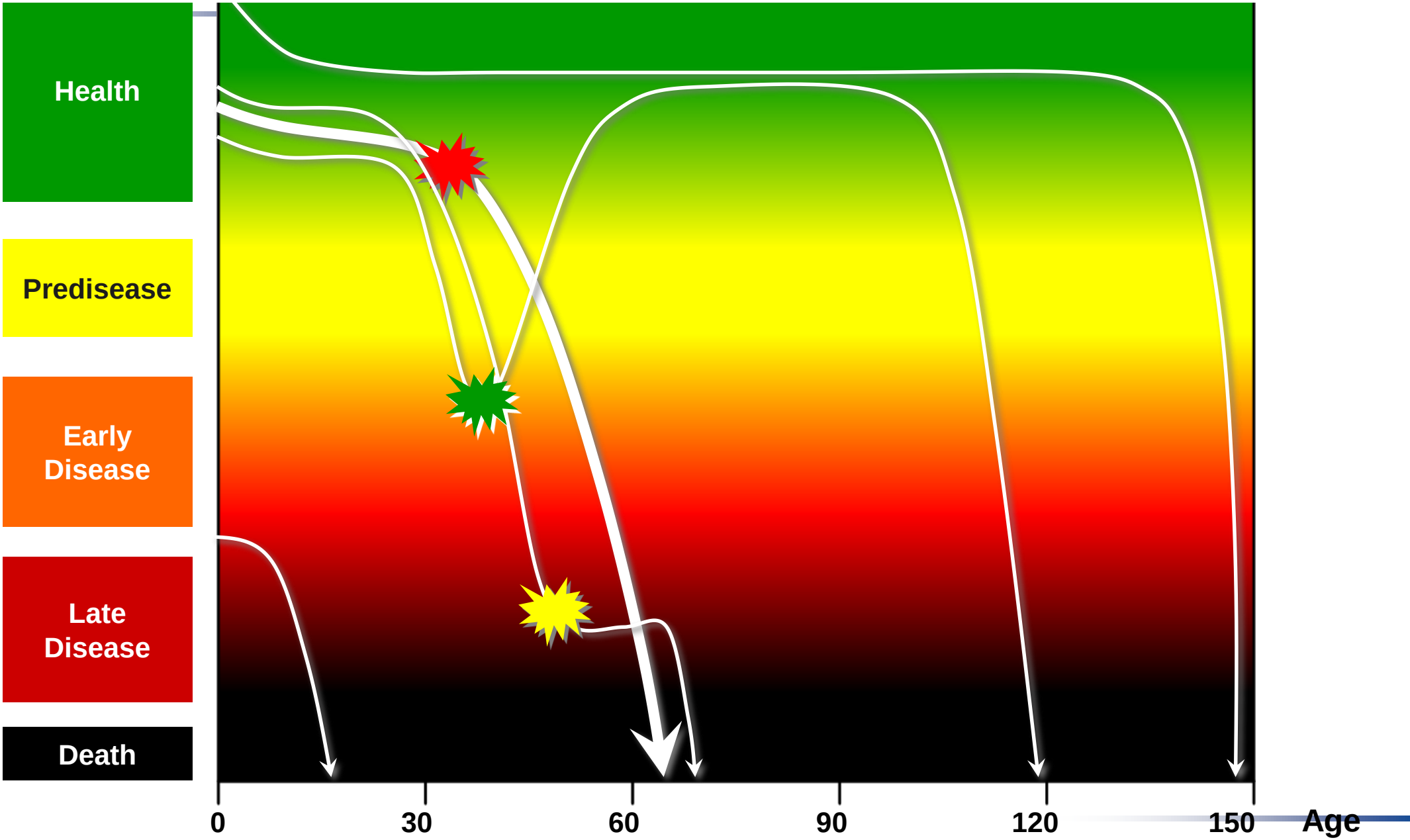
Integration of genome medicine with microbiome medicine基因组医学与微生物组医学（微生态医学）比翼双飞的时代来临了



From Genome Medicine to Microbiome Medicine

Eat Right, Keep Fit, Live Long, Die Quick

身材苗条、饮食适度、活得长寿、死得快速



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