Metabolomics and Genomics. Tools for nutritional molecular diagnostics.

1. What is Metabolomics?

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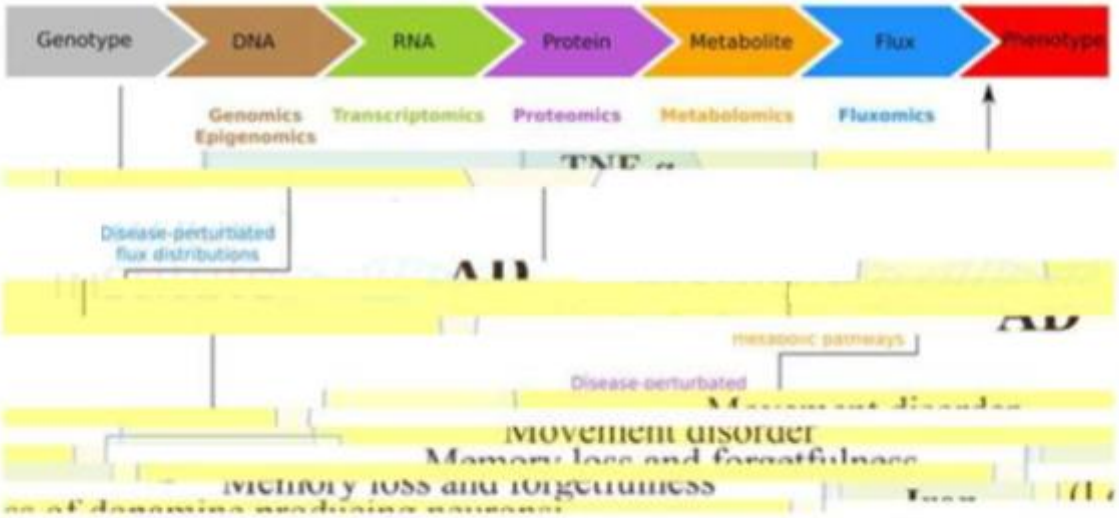

Front. Physiol., 09 December 2015

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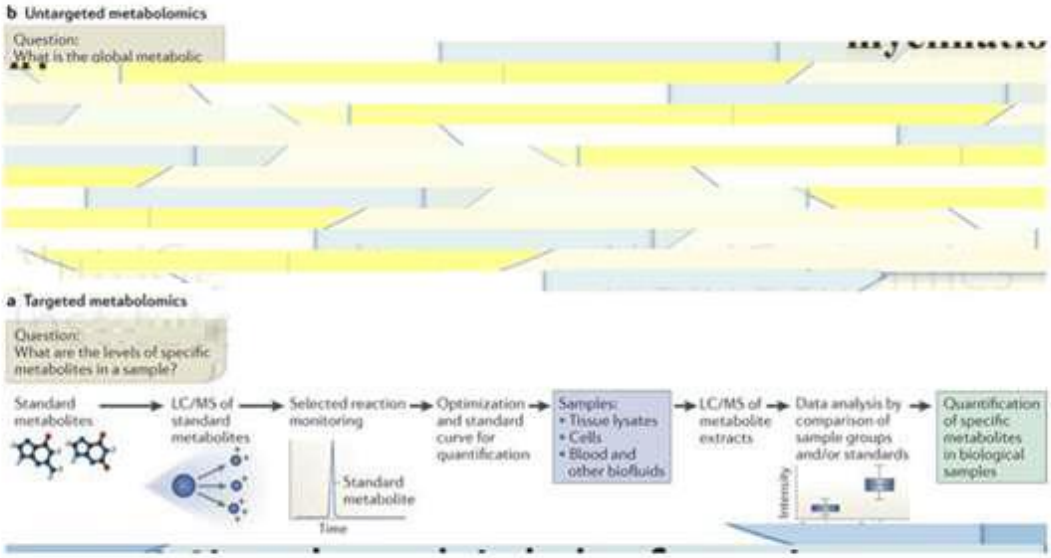

Nature Reviews Molecular Cell Biology 13, 263-269 (April 2012)

1. What is Metabolomics?

	NMR	MS
Sensitivity	Low but suboptimal	High
Selectivity	usually NON-selective	Both directed and non-directed
Sample measure	A single measure can detect the NMR-observable metabolites present	Different chromatography techniques needed for different types of metabolites
Sample recovery	Non-destructive	Destructive, but small amounts are used
Repeatibility	Very high	Moderate
Sample preparation	Minimal	Different columns and optimization of ionization needed
Tissue samples	Yes	No
Number of detectable metabolites in an urine sample	40-200	More than 500
Targeted analysis	Non-ideal	Ideal
In vivo studies	Yes	No

Methods Mol Biol. 2015;1277:161-93.

1. What is Metabolomics?

- Monitoring of enzyme kinetics and metabolic pathways
- **Monitoring of gene-environment interactions**
- Identification of unknown functions of genes and proteins
- **Tracking of effects of nutrients, toxins and drugs**
- **Generation of metabolic profiles for pathological conditions**
- **Having a general overview of the metabolism and the different treatments**
- **Expediting assessments and diagnoses**
- **More rapid, accurate and economical assessment and identification of pathological conditions**
- **Rapid assessment of the effects of a wide range of interventions, from sport to surgery**

Methods Mol Biol. 2015;1277:161-93.

2. Nutrigenomics, Metabolomics and diet. Genotype-phenotype relationship and nutritional treatments.

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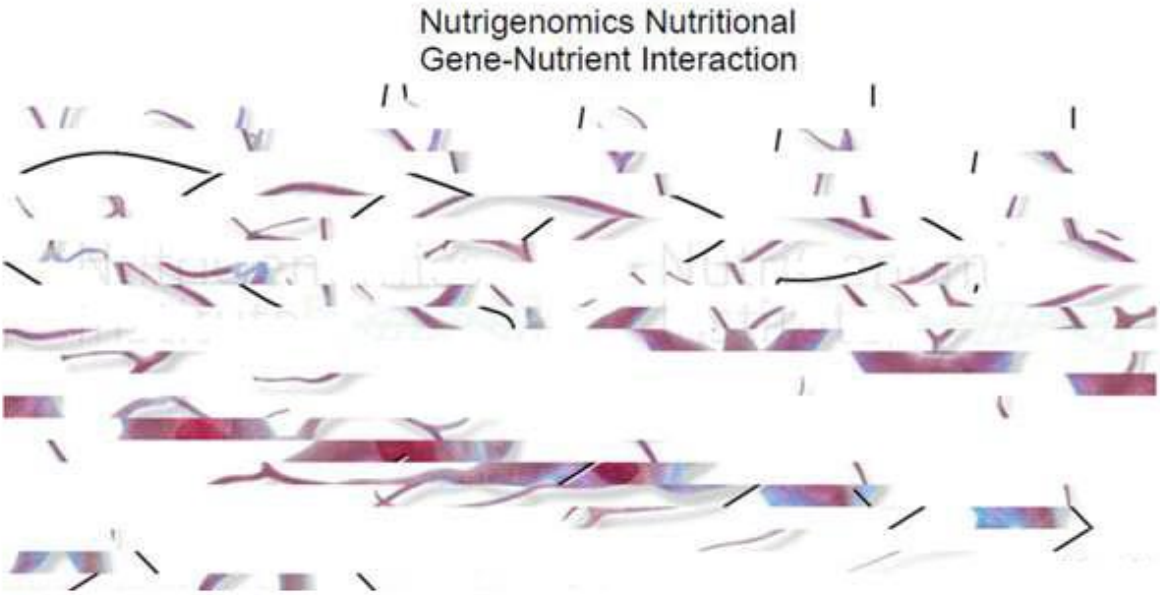

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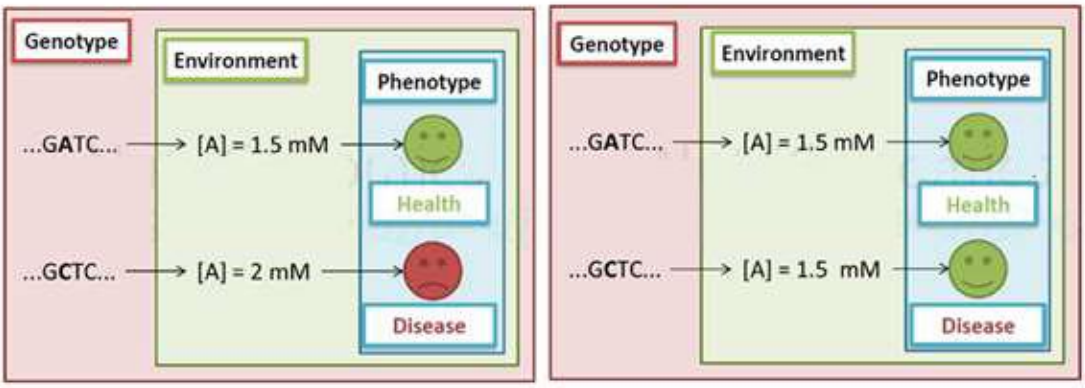

Adapted from Biochemical Society Transactions Nov 27, 2015, 43 (6) 1172-1176

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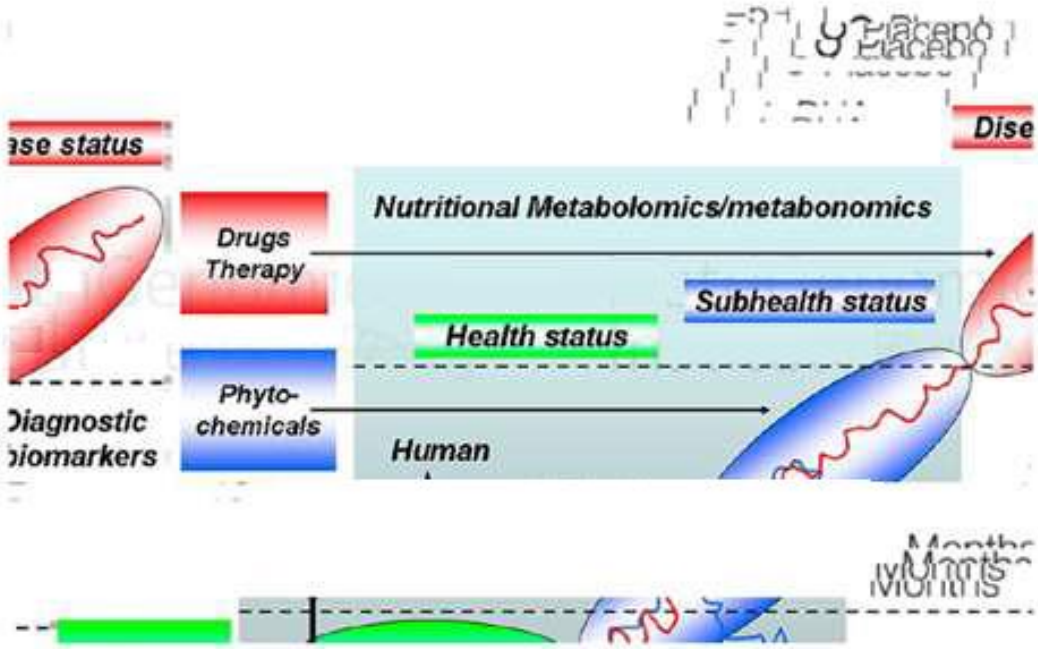


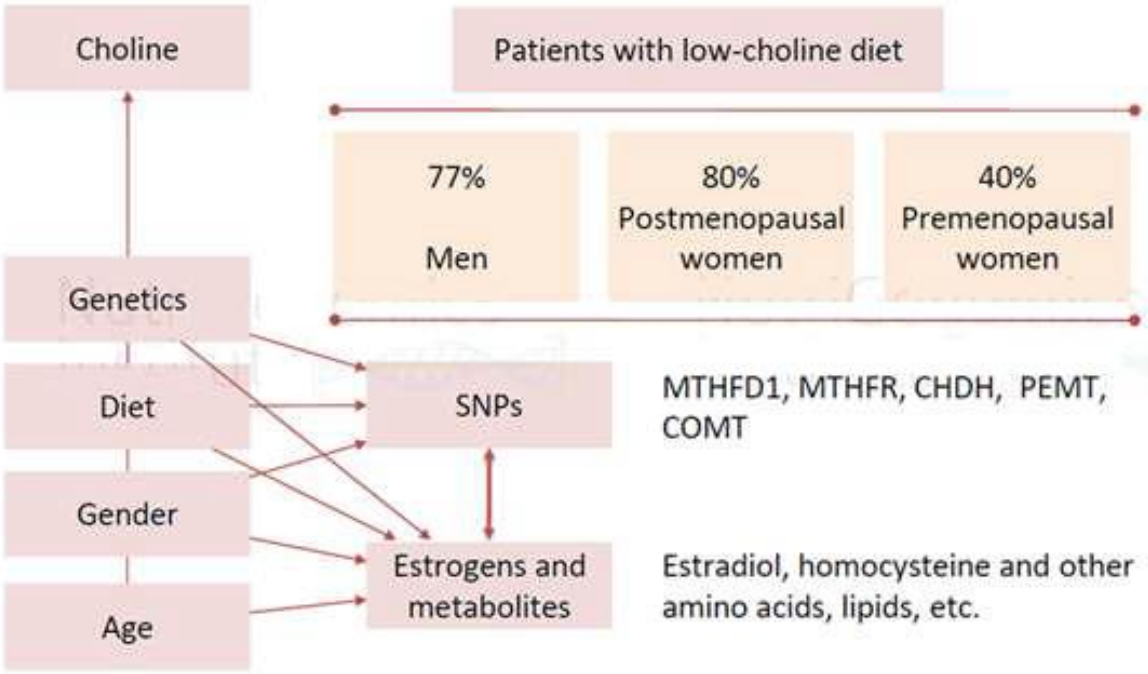
3. Role of Metabolomics in the identification of responders and non-responders.

3. Role of Metabolomics in the identification of responders and non-responders.

- How to identify before or during an intervention or treatment which subjects will respond favourably without having to wait for the final outcome?

- Genetic information can help identify who needs to ensure adequate intakes of a certain nutrient, and so does Metabolomics.

3. Role of Metabolomics in the identification of responders and non-responders.



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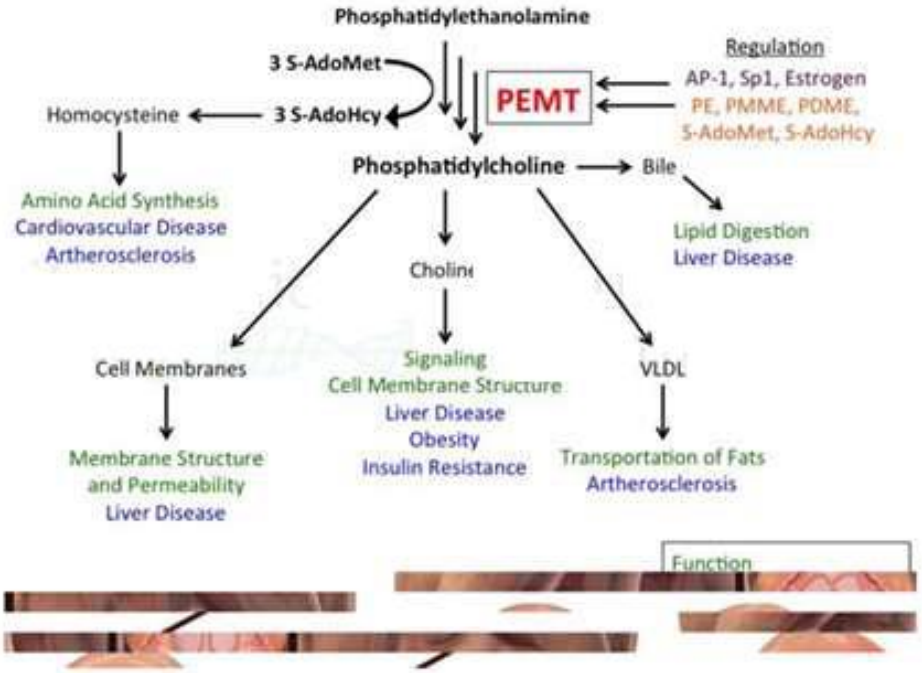


4. Metabolic profiling as a diagnostic tool.

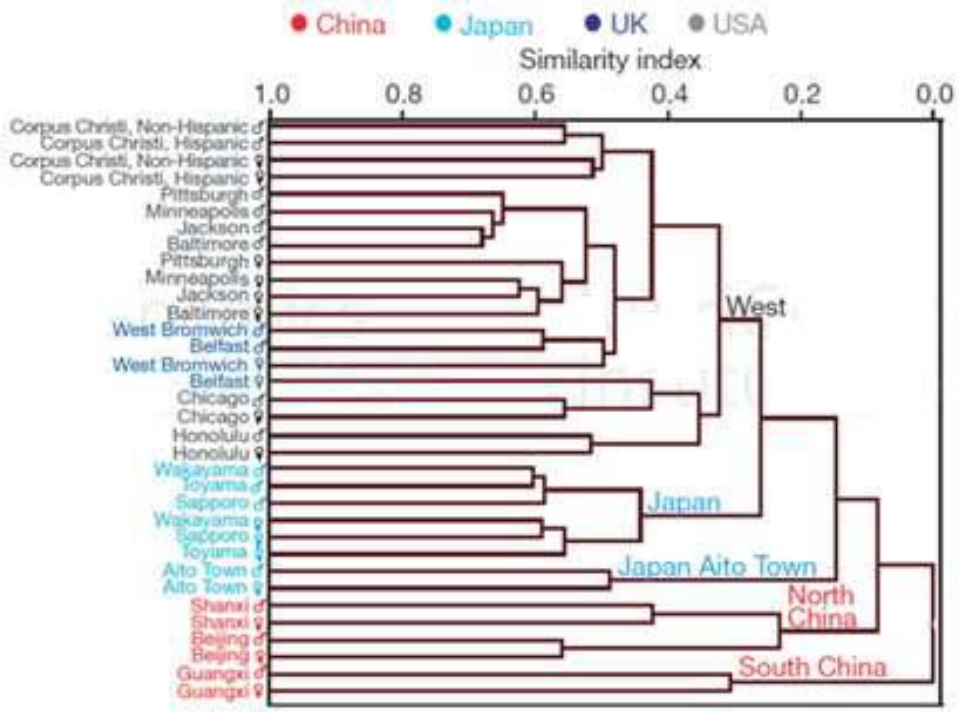
4. Metabolic profiling as a diagnostic tool.

- What shared and differential mechanisms among individuals from different populations defined by geographical or dietary criteria can cause certain diseases?

- In
  - What?
    - Mechanisms behind the global problem of blood pressure and diseases associated with it.
  - Why?
    - High blood pressure is a public health problem.
    - Reducing sodium intake campaigns are carried out, but sodium intake is still high. What sodium sources or mechanisms that alter its balance are there in the diet?How?
    - Metabolic phenotyping strategies
    - Different populations with different genetic background and lifestyle

Circulation. 2009 Jul 21; 120(3): 221–228.

4. Metabolic profiling as a diagnostic tool.



4. Metabolic profiling as a diagnostic tool.

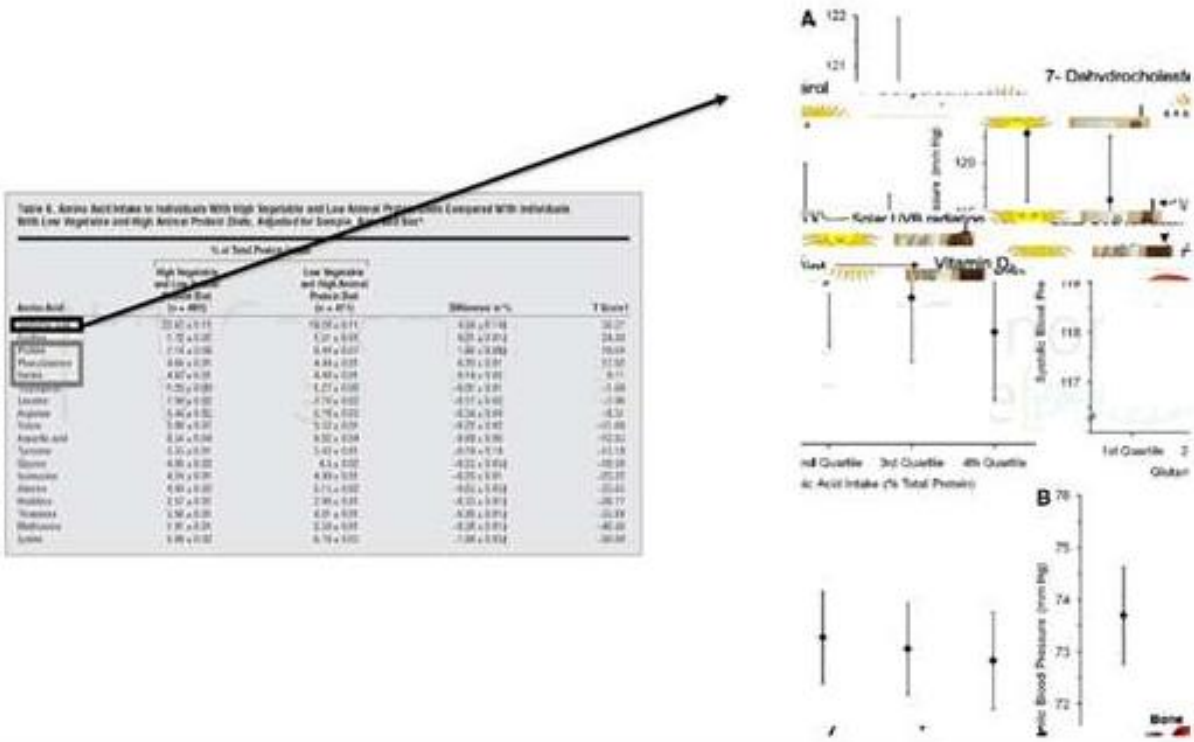
What dietary factors are evident in individuals with high blood pressure?

4. Metabolic profiling as a diagnostic tool.

Table 6. Amino Acid Intake in Individuals With High Vegetable and Low Animal Protein Diets Compared With Individuals With Low Vegetable and High Animal Protein Diets, Adjusted for Sample, Age, and Sex*

	% of Total Protein Intake			
Amino Acid	High Vegetable and Low Animal Protein Diet (n = 491)	Low Vegetable and High Animal Protein Diet (n = 471)	Difference in %	T Score†
Glutamic acid	22.67 ± 0.11	18.28 ± 0.11	4.39 ± 0.14‡	30.27
Cystine	1.72 ± 0.01	1.51 ± 0.01	0.21 ± 0.01‡	24.50
Proline	7.14 ± 0.06	5.49 ± 0.07	1.66 ± 0.08‡	19.64
Phenylalanine	4.64 ± 0.01	4.44 ± 0.01	0.20 ± 0.01	17.02
Serine	4.62 ± 0.01	4.48 ± 0.01	0.14 ± 0.02	9.11
Tryptophan	1.25 ± 0.00	1.27 ± 0.00	-0.01 ± 0.01	-1.68
Leucine	7.59 ± 0.02	7.76 ± 0.02	-0.17 ± 0.02	-7.06
Arginine	5.44 ± 0.03	5.78 ± 0.03	-0.34 ± 0.04	-9.31
Valine	5.09 ± 0.01	5.32 ± 0.01	-0.22 ± 0.02	-11.69
Aspartic acid	8.34 ± 0.04	9.02 ± 0.04	-0.68 ± 0.05	-12.53
Tyrosine	3.33 ± 0.01	3.52 ± 0.01	-0.19 ± 0.10	-13.18
Glycine	4.95 ± 0.02	4.5 ± 0.02	-0.55 ± 0.03‡	-18.59
Isoleucine	4.24 ± 0.01	4.49 ± 0.01	-0.25 ± 0.01	-23.22
Alanine	4.50 ± 0.02	5.13 ± 0.02	-0.63 ± 0.03‡	-23.63
Histidine	2.57 ± 0.01	2.90 ± 0.01	-0.33 ± 0.01‡	-26.77
Threonine	3.56 ± 0.01	4.01 ± 0.01	-0.45 ± 0.01‡	-33.84
Methionine	1.91 ± 0.01	2.30 ± 0.01	-0.38 ± 0.01‡	-40.56
Lysine	5.09 ± 0.02	6.75 ± 0.03	-1.68 ± 0.03‡	-50.68

4. Metabolic profiling as a diagnostic tool.



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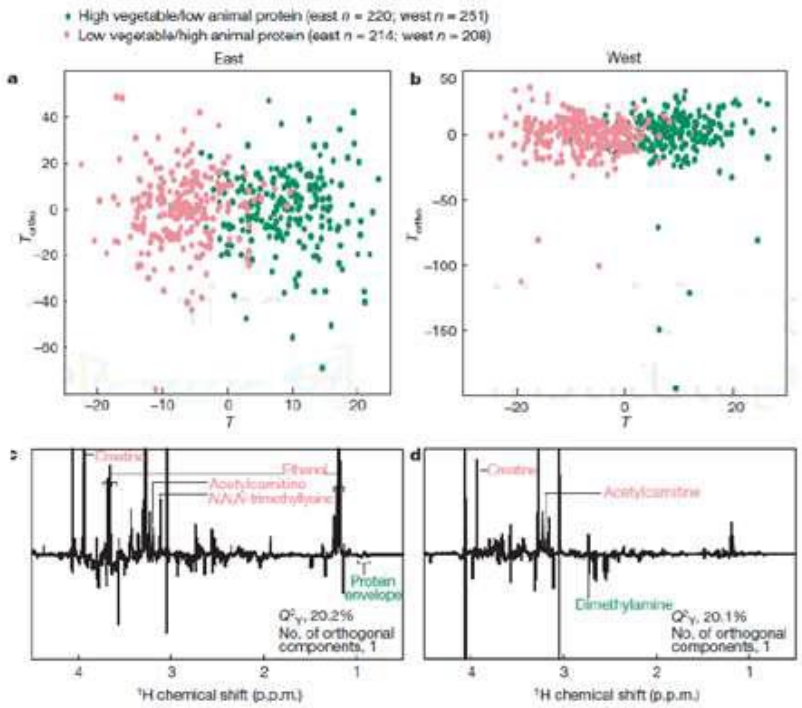

4. Metabolic profiling as a diagnostic tool.

- What does INTERMAP study allow us to do?

- Knowing which and how certain components derived from the diet or the microbiota affect such a pathophysiological process as hypertension.
- Searching for associated metabolites in patients with hypertension or at risk of hypertension in order to create subgroups and detect early changes.
- Implementing the results in dietary interventions which allow to change these metabolites in a direct way (such as increasing the ratio between vegetable and animal protein) or in an indirect way (such as through prebiotics and probiotics which favor a certain type of microbiota).
- Monitoring the results of the inverventions and adapting them to each individual.

5. Examples of metabolic profiles for medical diagnosis.

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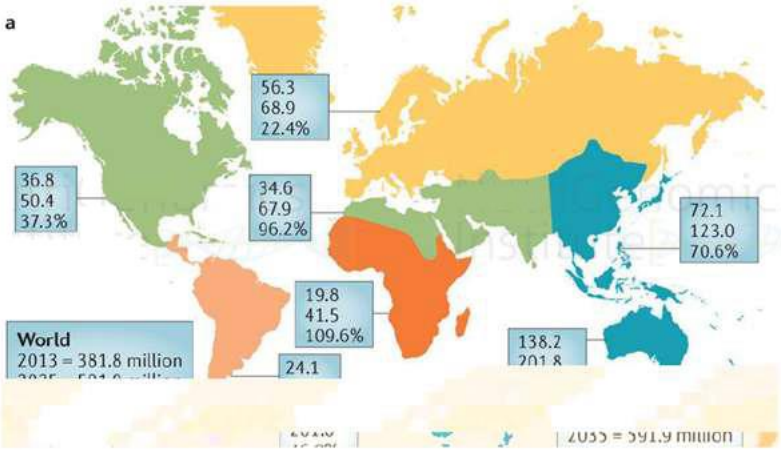


Nature Reviews Endocrinology 8, 228-236 (April 2012)

5. Examples of metabolic profiles for medical diagnosis.

Type 2 diabetes mellitus

Table 1: Diagnostic reference values

Parameters	Normal[*]	Prediabetes	T2DM
Haemoglobin A1c	<5.7%[‡] <6.0%[§]	5.7–6.4%[‡] 6.0–6.4%[§]	≥6.5%
Fasting plasma glucose	<100 mg per dl[‡] <110 mg per dl[§]	100–125 mg per dl[‡] 110–125 mg per dl[§]	≥126 mg per dl
Two-hour plasma OGTT	<140 mg per dl	140–199 mg per dl	≥200 mg per dl

1.OGTT, oral glucose tolerance test; T2DM, type 2 diabetes mellitus.
2.[*]Normal glucose metabolism.
3.[‡]American Diabetes Association.
4.[§]World Health Organization.

5. Examples of metabolic profiles for medical diagnosis.

- **Plasma Free Amino Acid Profiles Predict Four-Year Risk of Developing Diabetes, Metabolic Syndrome, Dyslipidemia, and Hypertension in Japanese Population**
  - Sci Rep. 2015; 5: 11918.

- **Plasma amino acid profiles are associated with insulin, C-peptide and adiponectin levels in type 2 diabetic patients.**
  - Nutr Diabetes. 2014 Sep 1;4:e133.

- **Weight loss is associated with plasma free amino acid alterations in subjects with metabolic syndrome**
  - Nutr Diabetes. 2016 Feb; 6(2): e197.

- **A Branched-Chain Amino Acid-Related Metabolic Signature that Differentiates Obese and Lean Humans and Contributes to Insulin Resistance**
  - Cell Metab. 2009 Apr;9(4):311-26.

- **Metabolite Profiles and the Risk of Developing Diabetes**
  - Nat Med. 2011 Apr; 17(4): 448–453.

- **Metabolic Signatures of Insulin Resistance in 7,098 Young Adults**
  - Diabetes. 2012 Jun; 61(6): 1372–1380.

- **Branched-Chain and Aromatic Amino Acids Are Predictors of Insulin Resistance in Young Adults**
  - Diabetes Care. 2013 Mar; 36(3): 648–655.

- **Circulating Metabolite Predictors of Glycemia in Middle-Aged Men and Women**
  - Diabetes Care. 2012 Aug; 35(8): 1749–1756.

- **Branched-chain amino acid catabolism fuels adipocyte differentiation and lipogenesis**
  - Nature Chemical Biology 12, 15–21 (2016)

- **Branched-Chain Amino Acids and Insulin Metabolism: The Insulin Resistance Atherosclerosis Study (IRAS).**
  - Diabetes Care. 2016 Apr;39(4):582-8.

- **A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance.**
  - Cell Metab. 2009 Apr;9(4):311-26.

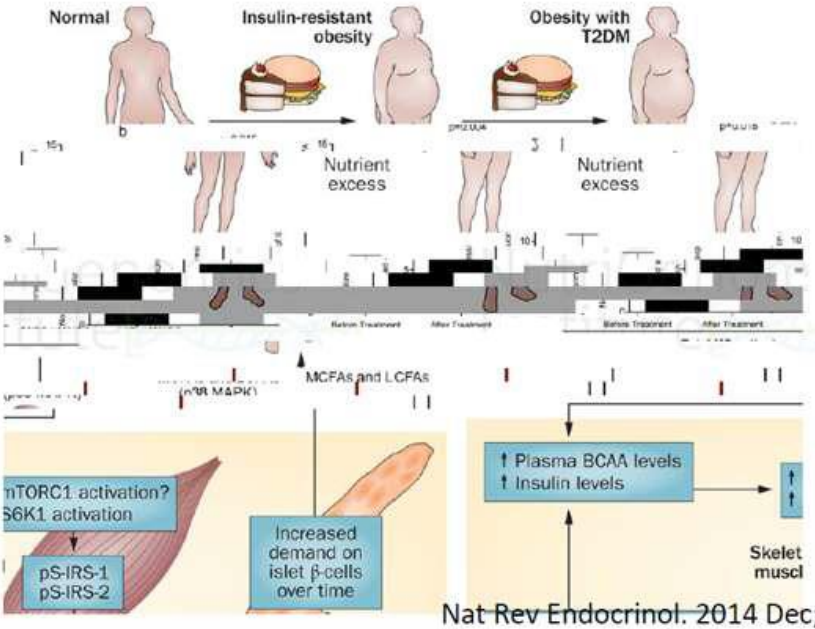
5. Examples of metabolic profiles for medical diagnosis.

Metabolite	Men β (SE)	Men P	Women β (SE)	Women P	$P_{sex\ interaction}$	Molecular link to insulin resistance
Branched-chain amino acids						Essential amino acids; phosphorylation of insulin receptor substrate-1 and the mammalian target of rapamycin complex (9,10,27,31–33)
Leu	0.14 (0.015)	9×10^{-21}	0.082 (0.015)	5×10^{-8}	6×10^{-4}	
Ile	0.22 (0.019)	2×10^{-31}	0.11 (0.017)	5×10^{-12}	0.006	
Val	0.14 (0.015)	4×10^{-21}	0.097 (0.015)	5×10^{-11}	0.004	
Aromatic amino acids						Precursor for neurotransmitters; thyroid function (10,27,28)
Phe	0.17 (0.017)	5×10^{-23}	0.18 (0.015)	5×10^{-29}	0.25	
Tyr	0.21 (0.016)	1×10^{-37}	0.044 (0.015)	0.003†	2×10^{-11}	
Glycolysis and gluconeogenesis intermediates						Gluconeogenesis and glycolysis; nitric oxide; transamination (28,43,44)
Ala	0.24 (0.016)	9×10^{-50}	0.16 (0.015)	1×10^{-28}	6×10^{-5}	
Gln	−0.082 (0.017)	1×10^{-6}‡	−0.11 (0.015)	2×10^{-13}	0.86	
Lactate	0.17 (0.016)	7×10^{-27}	0.13 (0.014)	2×10^{-20}	0.24	
Pyruvate	0.21 (0.016)	2×10^{-44}	0.21 (0.014)	4×10^{-50}	0.92	
Ketone bodies						Ketogenesis; fatty acid oxidation (47,48)
Acetoacetate	−0.17 (0.014)	4×10^{-35}	−0.19 (0.014)	1×10^{-37}	1×10^{-4}	
3-hydroxybutyrate	−0.13 (0.013)	2×10^{-23}‡	−0.079 (0.014)	6×10^{-7}	6×10^{-3}	
Glycoproteins						Low-grade inflammation (47)
α1-acid glycoprotein	0.11 (0.02)	7×10^{-13}	0.15 (0.018)	4×10^{-16}	0.50	
Fatty acids						Energy storage; lipid transport; precursors of prostaglandins and endocannabinoids; free fatty acid–mediated insulin resistance; impairment of fatty acid oxidation (7,8,7)
Total	0.21 (0.019)	5×10^{-8}	0.35 (0.030)	2×10^{-13}	0.23	
n3	0.025 (0.016)	0.12†	0.057 (0.015)	4×10^{-4}	0.16	
n6 and n7	0.092 (0.026)	0.01†	0.22 (0.030)	7×10^{-13}	0.06	
n9 and saturated	0.19 (0.022)	5×10^{-9}	0.25 (0.029)	2×10^{-17}	0.06	
Phospholipids						Membrane and lipoprotein composition; cellular signaling (48)
Phosphocholines	0.17 (0.020)	2×10^{-8}	0.17 (0.030)	8×10^{-6}‡	0.84	
Phosphoglycerides	0.15 (0.024)	5×10^{-7}	0.15 (0.034)	7×10^{-6}‡	0.92	
Fatty acid saturation measures						Fatty acid saturation and chain length (11)
Average number of methylene groups per double bond	0.11 (0.018)	1×10^{-9}	0.073 (0.016)	7×10^{-6}‡	0.50	
Average number of double bonds per fatty acid chain	−0.098 (0.018)	1×10^{-7}	−0.078 (0.018)	2×10^{-6}‡	0.72	

β-Regression coefficients (SE) are in units of 1 SD HOMA-IR per 1 SD change in metabolite concentration. The associations were adjusted for age, waist circumference, total cholesterol, HDL cholesterol, and triglycerides. Associations were meta-analyzed for the NFBC and the YFS (n = 7,098). Metabolites were denoted significant at $P < 0.005$. †Nominally significant in one of the cohorts only.

- Branched-chain amino acids
- Aromatic amino acids
- Glycolysis and gluconeogenesis intermediates
- Ketone bodies
- Glycoproteins
- Fatty acids
- Phospholipids
- Fatty acid saturation

5. Examples of metabolic profiles for medical diagnosis.



Nat Rev Endocrinol. 2014 Dec;10(12):723-36

6. Examples of the relationship between nutritional treatment and changes in metabolic profiles

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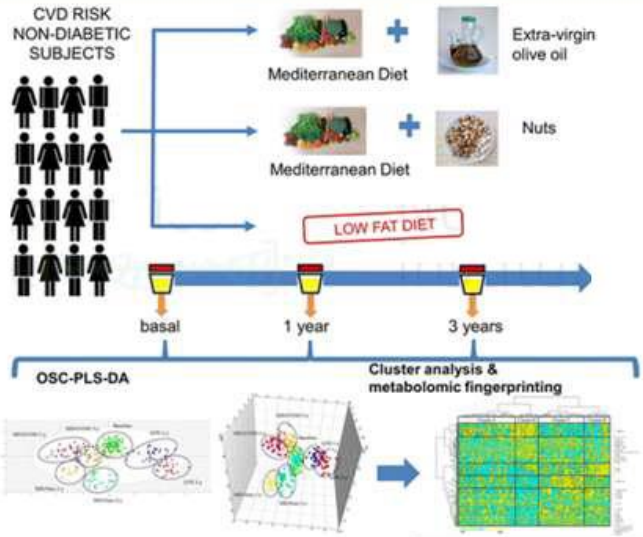
PREDIMED Study



6. Examples of the relationship between nutritional treatment and changes in metabolic profiles.

MD associated metabolites	1-year ANCOVA (p)			3-year ANCOVA (p)		
metabolite ID	E vs L	N vs L	E vs N	E vs L	N vs L	E vs N
3-HB	↑*	↑*	-	↑*	↑*	-
leucine	↑*	↑*	-	↑*	↑*	-
isobutyric acid[§,#]	↑*	↑*	-	↑*	↑*	-
2-oxoisovaleric[⊥,†]	-	-	-	↑*	-	-
4-DTEA[◊]	↑*	↑*	-	↑*	↑*	-
N-Ac[‡]	↑*	-	-	↑*	-	-
glycine	-	-	-	↑	↑	-
p-cresol[#]	↑*	-	-	-	↑*	↓*
suberic acid	↑*	↑*	-	↑*	↑*	↓*
oleic acid	↑*	↑*	-	↑*	↑*	-
proline	↑*	↑*	-	↑*	↑*	-
U3.46	↑*	↑	-	↑*	↑*	-
U3.33	-	-	-	-	-	-
U3.50	-	-	-	↑*	↑*	-
U3.81	-	↑	-	↑*	↑*	-

J Proteome Res. 2015 Jan 2;14(1):531-40

6. Examples of the relationship between nutritional treatment and changes in metabolic profiles

Foodball project: http://foodmetabolome.org/

J Proteome Res. 2015 Jan 2;14(1):531-40

Nutrigenomics and neurodegenerative diseases.

Nutrigenomics and neurodegenerative diseases.

1. Introduction to neurodegenerative diseases
2. Molecular basis of neurodegenerative diseases
3. Nutrigenomics and Alzheimer's Disease (AD)
4. Nutrigenomics and Parkinson's Disease (PD)
5. Nutrigenomics and Multiple Sclerosis (MS)

1. Introduction to neurodegenerative diseases

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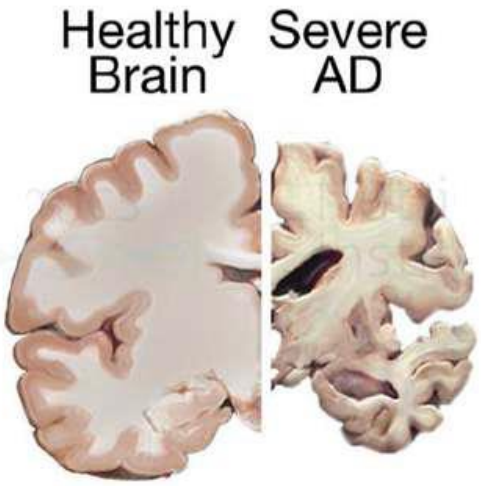


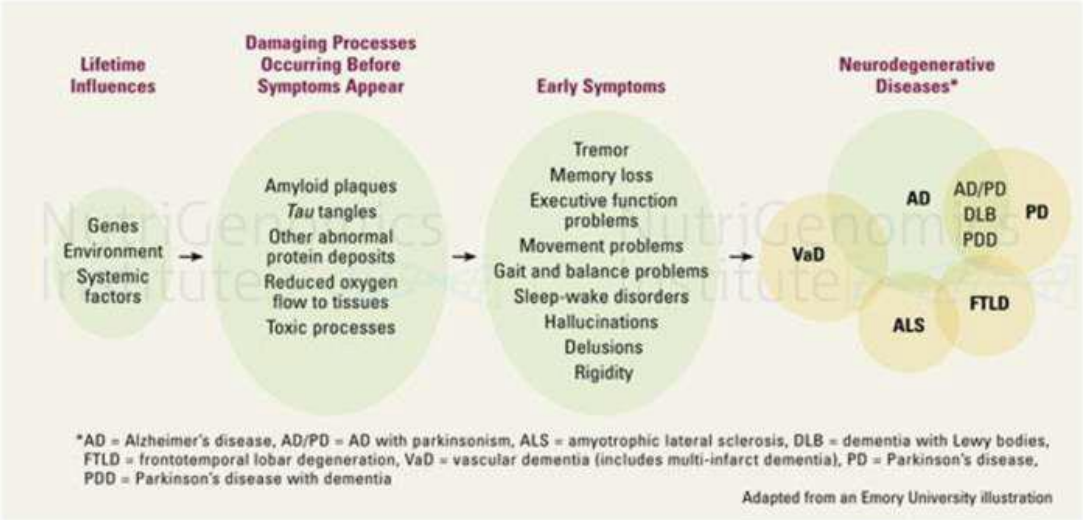
1. Introduction to neurodegenerative diseases

NEURODEGENERATIVE DISEASES CHARACTERIZED BY FILAMENTOUS-LESIONS FORMED FROM AGGREGATED PEPTIDES/PROTEINS

DISEASE	LESION/COMPONENTS	LOCATION
Alzheimer's Disease (AD)*	Senile Plaques/β-amyloid, NAC Neurofibrillary tangles/PHFτ	Extracellular Intracytoplasmic
Amyotrophic Lateral Sclerosis (ALS)	Spheroids/NF subunits	Intracytoplasmic
Dementia with Lewy Bodies (DLB)#	Lewy Bodies/NF subunits, α-synuclein	Intracytoplasmic
Lewy Body Variant Alzheimers Disease (AD + DLB)#	Senile Plaques/β-amyloid, NAC Neurofibrillary tangles/PHFτ Lewy Bodies/NF subunits, α-synuclein	Extracellular Intracytoplasmic Intracytoplasmic
Multiple System Atrophy (MSA)#	Glial Cell Inclusions/α-synuclein	Intracytoplasmic
Neuronal intranuclear inclusion disease	Inclusions/Expanded polyglutamine tracts	Intranuclear
Parkinson's Disease (PD)#	Lewy Bodies/NF subunits, α-synuclein	Intracytoplasmic
Prion diseases	Amyloid plaques/Prion	Extracellular
Tauopathies*	Neurofibrillary tangles/AD-like PHFτ	Intracytoplasmic
Tri-nucleotide repeat diseases	Inclusions/Expanded polyglutamine tracts	Intranuclear
Tri-nucleotide repeat diseases	Inclusions/Expanded polyglutamine tracts	Intranuclear

This table summarizes neurodegenerative disorders characterized by filamentous brain lesions in the extracellular space or within neurons or glia.
* AD is a heterogeneous dementing disorder, and one of several tauopathies. Other tauopathies are: progressive supranuclear palsy, Pick's Disease, corticobasal degeneration, FTDP-17 and Guam amyotrophic lateral sclerosis/parkinsonism dementia complex.
# Synuclein are implicated in diverse disorders known as synucleinopathies and AD is one as well. (From Trojanowski JQ, Goedert M, Iwatsubo T, Lee VM-Y. (1998) Fatal Attraction: Abnormal protein aggregation and neuron death in Parkinson's disease and Lewy body dementia. *Cell Death Diff*, **5**:832-837.)

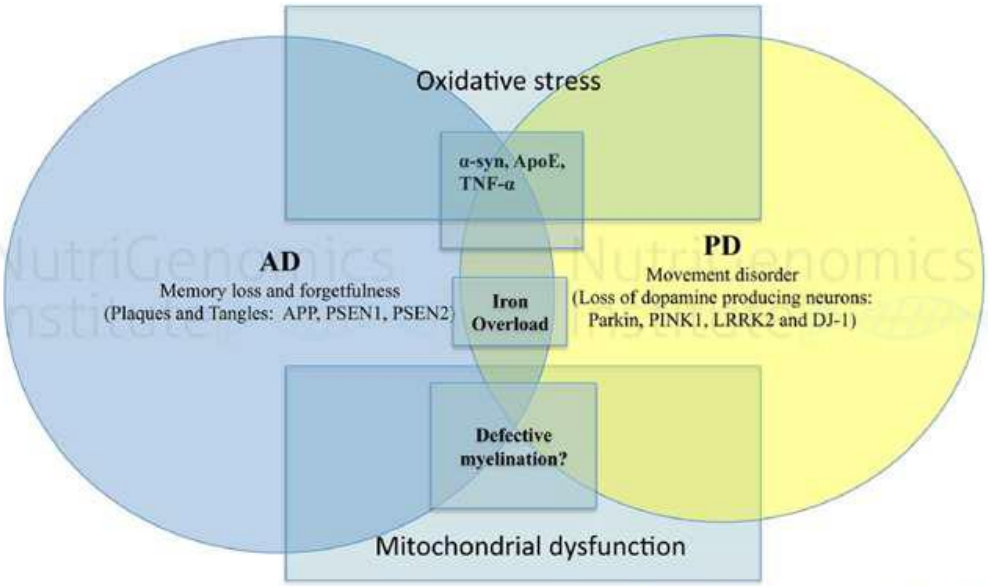
1. Introduction to neurodegenerative diseases



*AD = Alzheimer's disease, AD/PD = AD with parkinsonism, ALS = amyotrophic lateral sclerosis, DLB = dementia with Lewy bodies, FTLD = frontotemporal lobar degeneration, VaD = vascular dementia (includes multi-infarct dementia), PD = Parkinson's disease, PDD = Parkinson's disease with dementia

Adapted from an Emory University illustration

1. Introduction to neurodegenerative diseases



Front. Aging Neurosci., 21 July 2010

1. Introduction to neurodegenerative diseases.

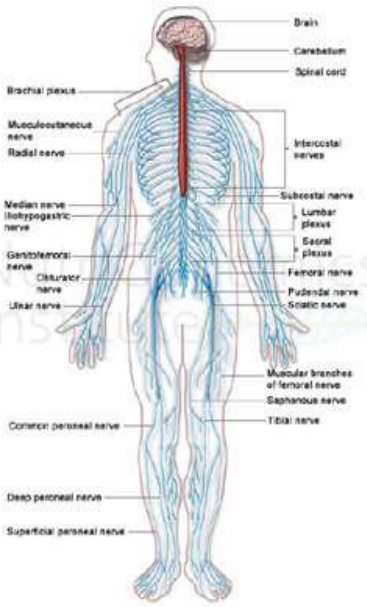
Disease	Cases per 100,000 population	Prevalence	Affected population
Alzheimer's Disease and other dementias	400	0.5 %	35.6 M
Parkinson's Disease	315	0.34 %	23.8 M
Multiple Sclerosis	30	0.03 %	2.28 M

Cause category	2005 (%)	2015 (%)	2030 (%)
Alzheimer and other dementias	0.73	0.81	0.92
Parkinson's disease	0.18	0.20	0.23
Multiple sclerosis	0.03	0.03	0.02

Prince et al., 2013; Pringsheim et al., 2014; Trisolini et al., 2010, WHO, 2006

1. Introduction to neurodegenerative diseases.

- Nervous System
  - Anatomical division
    - **CENTRAL NERVOUS SYSTEM** (brain, cerebellum, brain stem and spinal cord)
    - **PERIPHERAL NERVOUS SYSTEM** (nerves and neurons)
  - Functional division
    - **SOMATIC** (voluntary actions)
    - **AUTONOMIC** (involuntary actions)
  - Histology
    - Neuron (receiving stimuli and carrying nerve impulses)
    - Glia (Support and protection of neurons)



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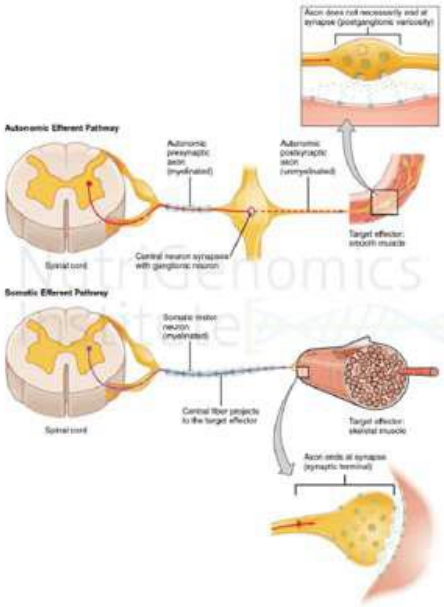

2. Molecular basis of neurodegenerative diseases

- Nervous System
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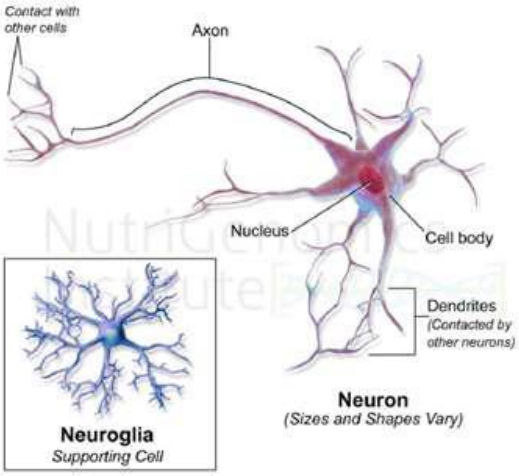
    - **NEURON** (receiving stimuli and carrying nerve impulses)
    - **GLIA** (Support and protection of neurons)



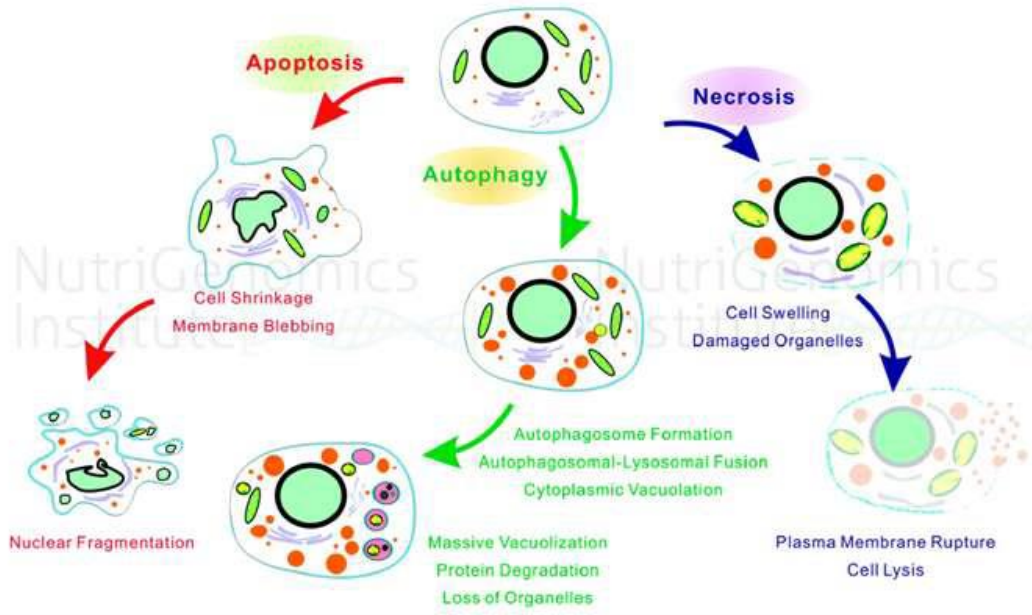
Neural Tissue

2. Molecular basis of neurodegenerative diseases

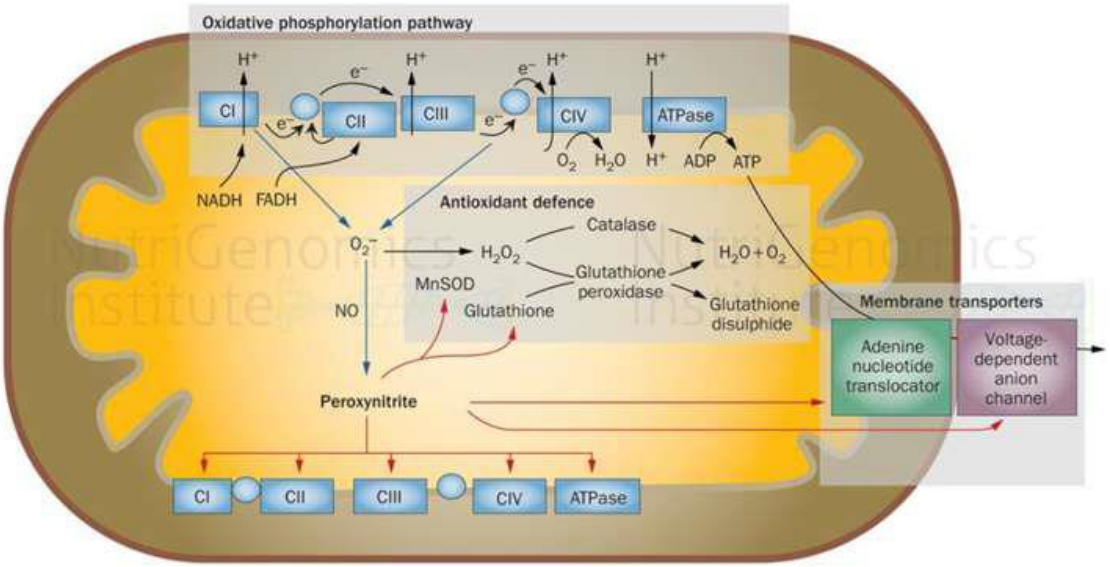
2. Molecular basis of neurodegenerative diseases

- Neuronal death; apoptosis and autophagy
- Oxidative stress and mitochondrial alterations; aging process
- Neuronal excitotoxicity; glutamate receptors and calcium channels.
- Neuroinflammation; the role of glia.
- Pro-inflammatory cytokines and and chemokines in the brain; Toll-like receptors, classical and alternative activation of inflammatory response.
- Protein aggregation and deposit

2. Molecular basis of neurodegenerative diseases

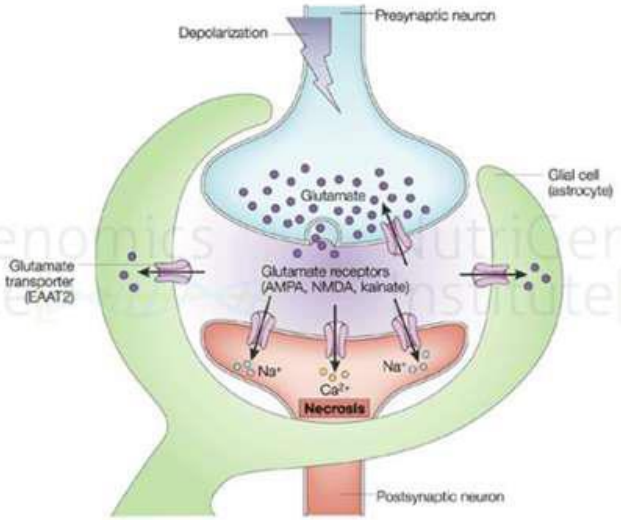


2. Molecular basis of neurodegenerative diseases



Nature Reviews Neurology 10, 326–336 (2014)

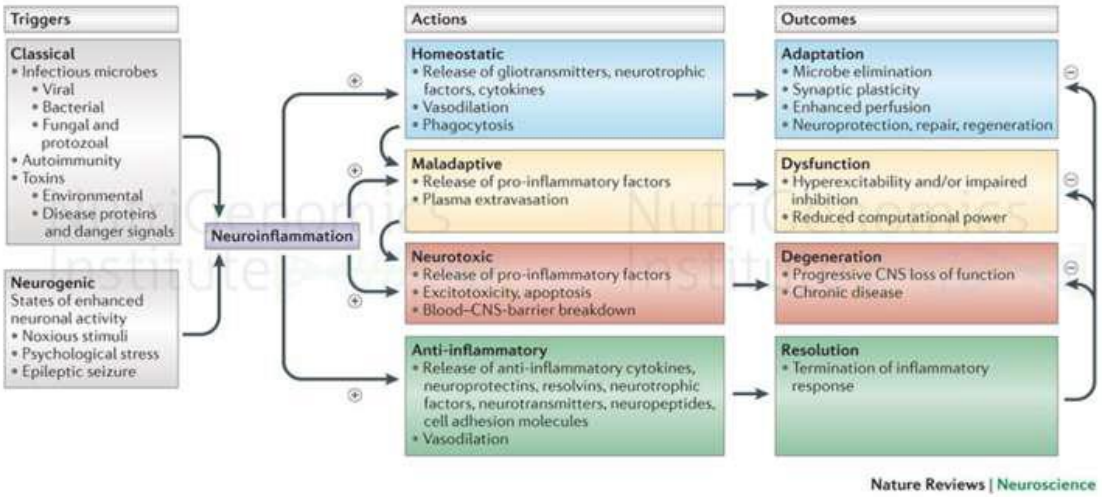
2. Molecular basis of neurodegenerative diseases



Nature Reviews | Neuroscience

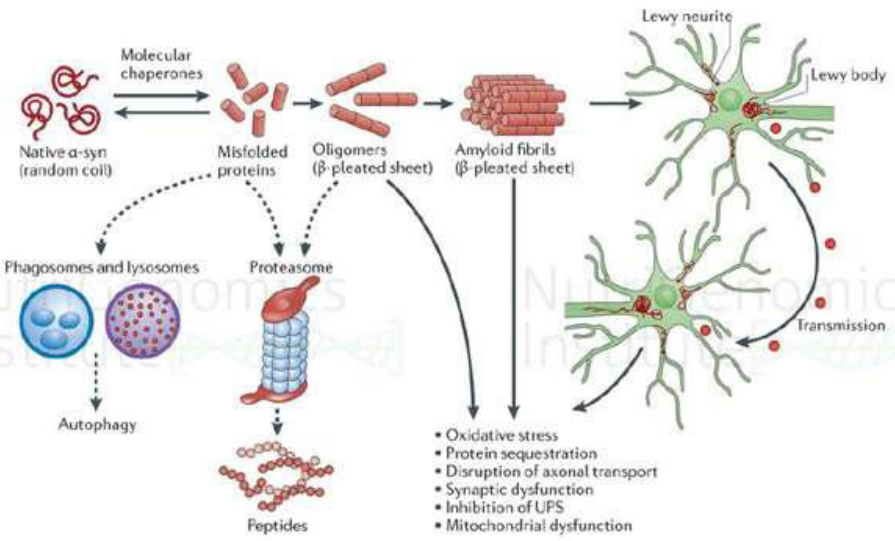
Nature Reviews Neuroscience 4, 672-684 (August 2003)

2. Molecular basis of neurodegenerative diseases



Nature Reviews Neuroscience 4, 672-684 (August 2003)

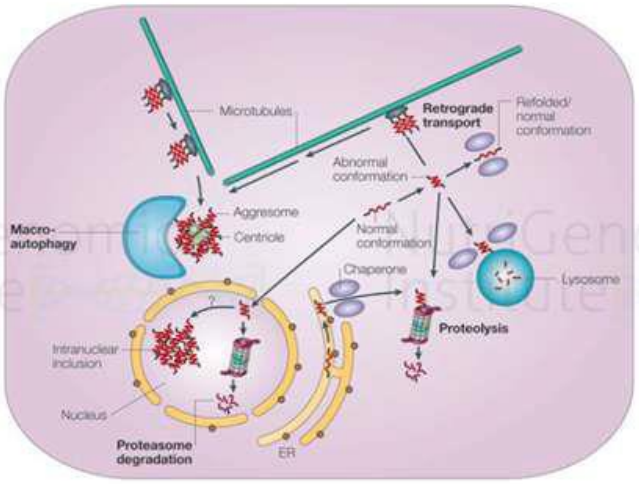
2. Molecular basis of neurodegenerative diseases



Nature Reviews | Neuroscience

Nature Reviews Neuroscience 14, 626–636 (2013)

2. Molecular basis of neurodegenerative diseases



Nature Reviews | Molecular Cell Biology

Nature Reviews Molecular Cell Biology 6, 891-898 (November 2005)

3. Nutrigenomics and Alzheimer's Disease (AD)

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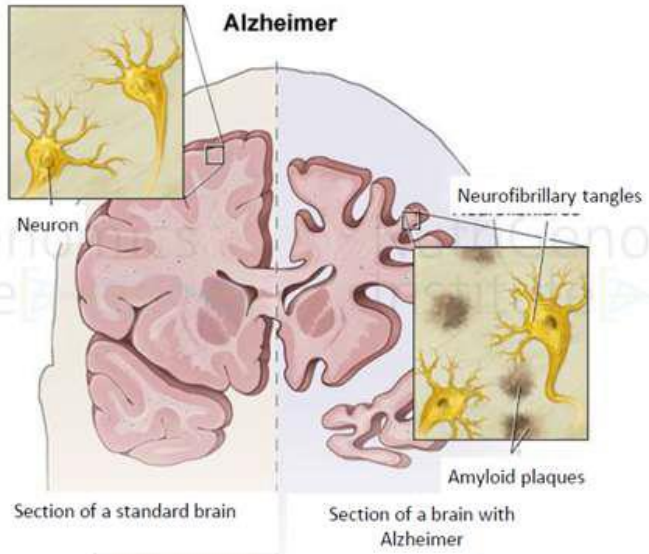
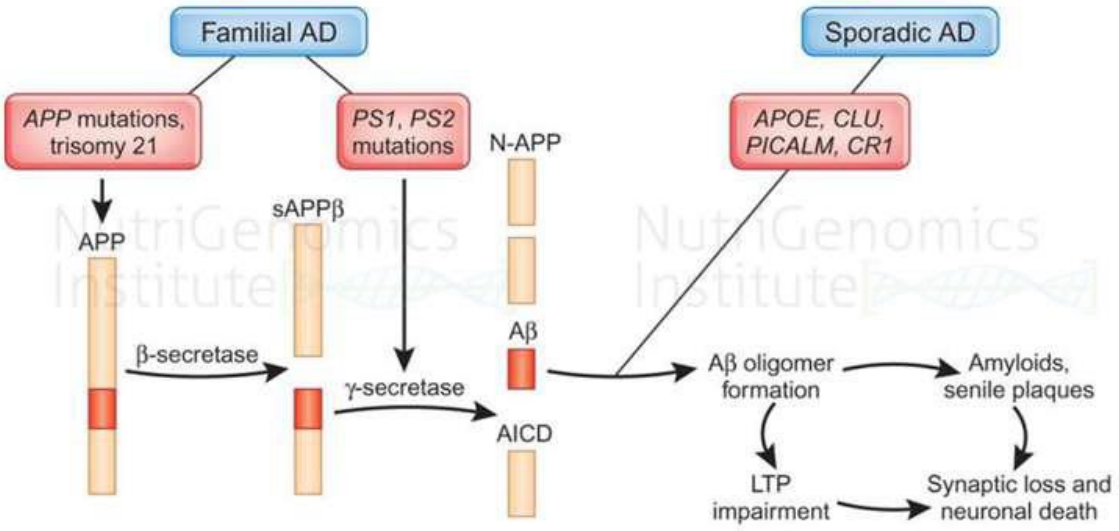


http://healthcare.utah.edu

3. Nutrigenomics and Alzheimer's Disease (AD)



Nature Genetics 41, 1047 - 1048 (2009)

3. Nutrigenomics and Alzheimer's Disease (AD)

Purpose in Life and Alzheimer's

A study suggests that having a greater purpose in life may help limit the harmful effects of changes in the brain associated with Alzheimer's disease.

Protective Plant Chemicals

Eating a rainbow of fruits and vegetables has the potential to keep your brain healthy and protect you from heart disease and cancer.

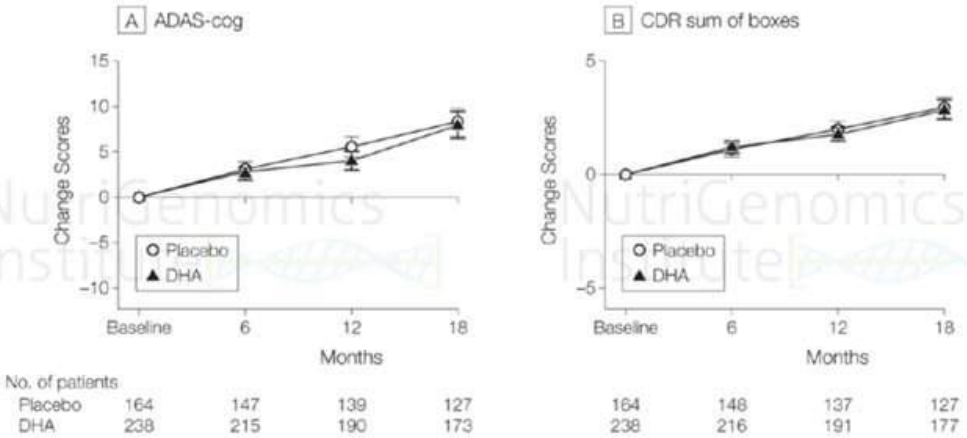
Make Your Diet Greener

With so many options, it's easy to make leafy greens a more prominent part of your plate — from side dishes to entrees.

https://www.nia.nih.gov

3. Nutrigenomics and Alzheimer's Disease (AD)

- ADAS-cog: cognitive subscale of the Alzheimer's Disease Assessment Scale
- CDR: Clinical Dementia Rating

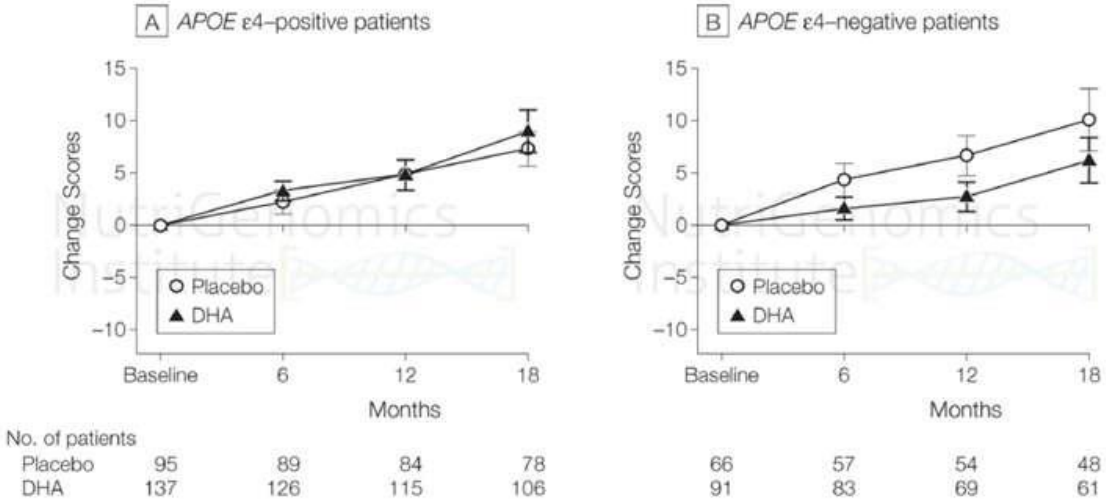


No. of patients

Placebo	164	147	139	127	164	148	137	127
DHA	238	215	190	173	238	216	191	177

JAMA. 2010;304(17):1903-1911.

3. Nutrigenomics and Alzheimer's Disease (AD)



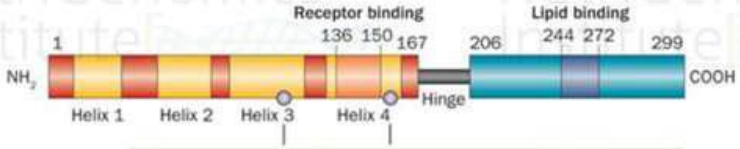
JAMA. 2010;304(17):1903-1911.

3. Nutrigenomics and Alzheimer's Disease (AD)

DHA

caprylic triglyceride

statins



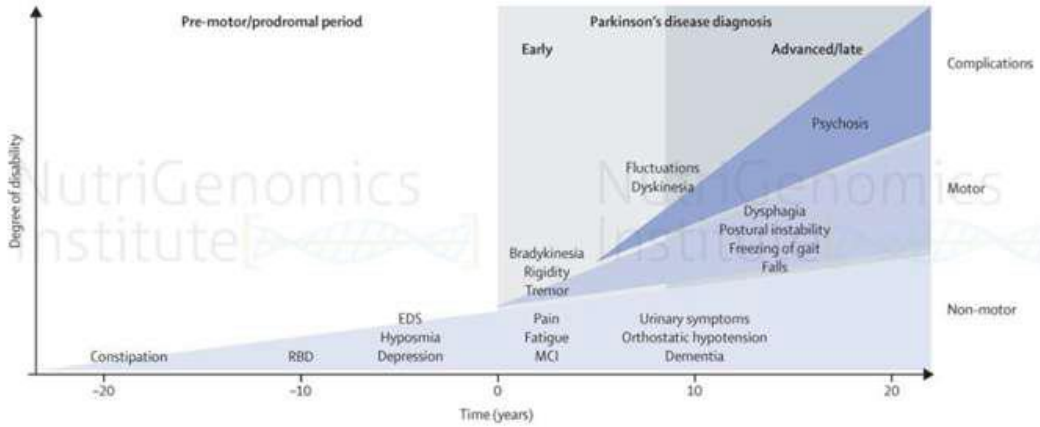
	Isoform-specific amino acid difference		Allele frequency (%)	
	112	158	General	AD
Apo-E2	Cys	Cys	8.4	3.9
Apo-E3	Cys	Arg	77.9	59.4
Apo-E4	Arg	Arg	13.7	36.7

Nature Reviews Neurology 9, 106-118 (February 2013)

4. Nutrigenomics and Parkinson's Disease (PD)

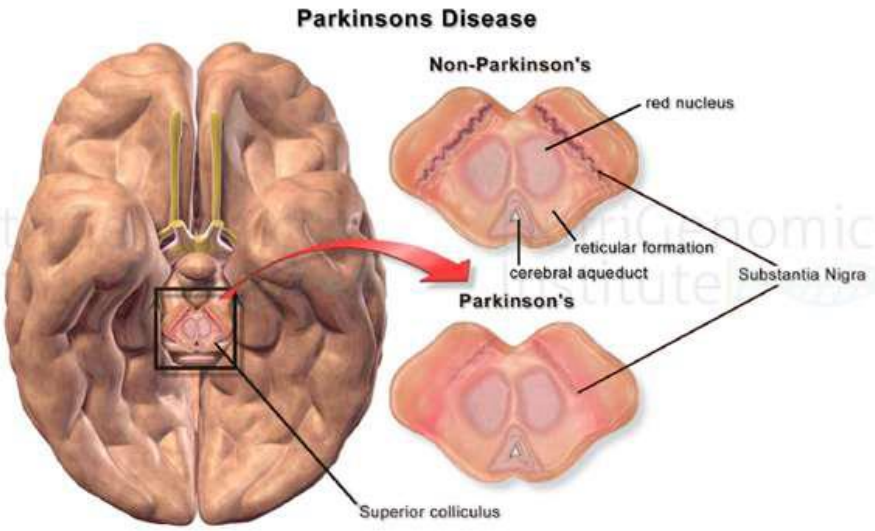
4. Nutrigenomics and Parkinson's Disease (PD)

EDS=excessive daytime sleepiness.
MCI=mild cognitive impairment.
RBD=REM sleep behaviour disorder.



The Lancet, Vol. 386, No. 9996, p896–912, 29 August 2015

4. Nutrigenomics and Parkinson's Disease (PD)



en.wikipedia.org

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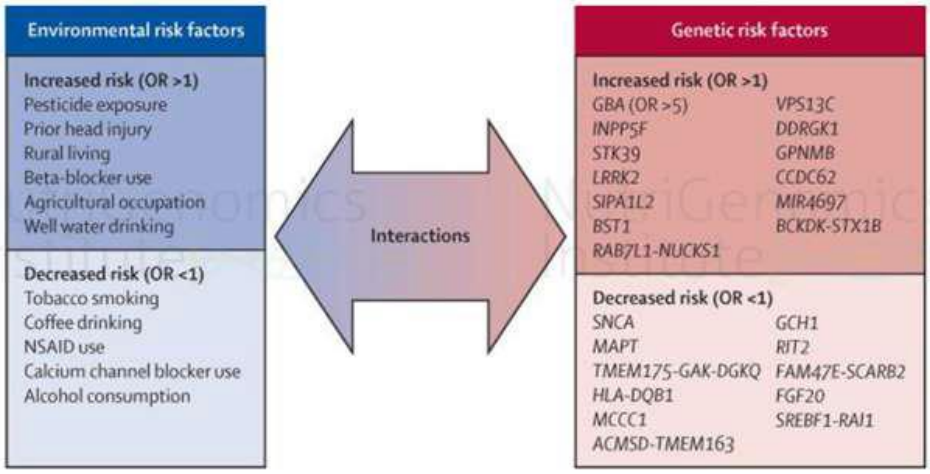

The Lancet, Vol. 386, No. 9996, p896–912, 29 August 2015

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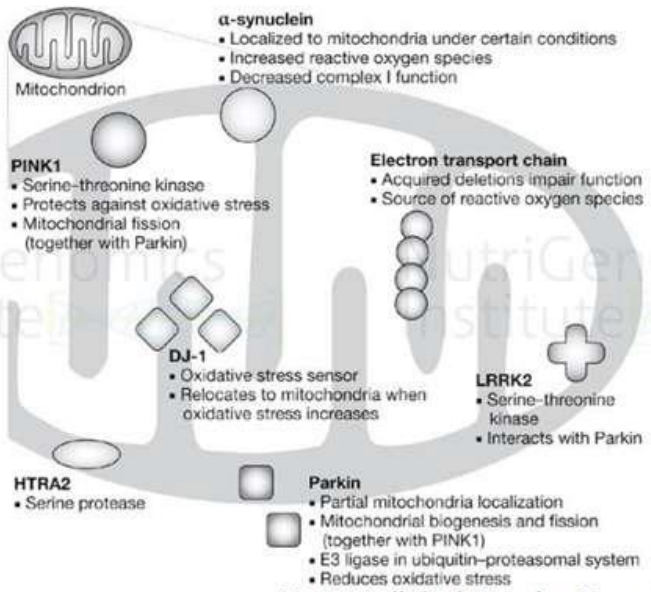

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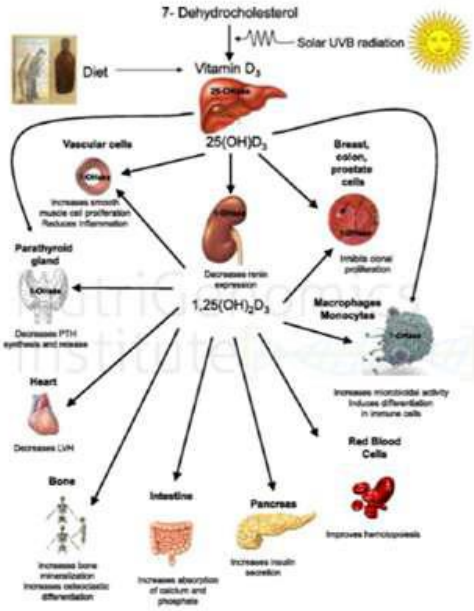
4. Nutrigenomics and Parkinson's Disease (PD)



Vitamin D receptor polymorphisms and Parkinson's disease in a Korean population: Revisited.
Kang SY, Park S, Oh E, Park J, Youn J, Kim JS, Kim JJ, Jang W.
Neurosci Lett. 2016 Aug 15;629:230-6. doi: 10.1016/j.neulet.2016.06.041. Epub 2016 Jun 21.
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Serum 25-hydroxyvitamin D concentrations in Mid-adulthood and Parkinson's disease risk.
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Mov Disord. 2016 Jul;31(7):972-9. doi: 10.1002/mds.26573. Epub 2016 Apr 19.
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Nutrients. 2016 Mar 29;8(4):186. doi: 10.3390/nu8040186. Review.
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American Journal of Physiology - Renal Physiology Dec 2009, 297 (6) F1502-F1509

5. Nutrigenomics and Multiple Sclerosis (MS)

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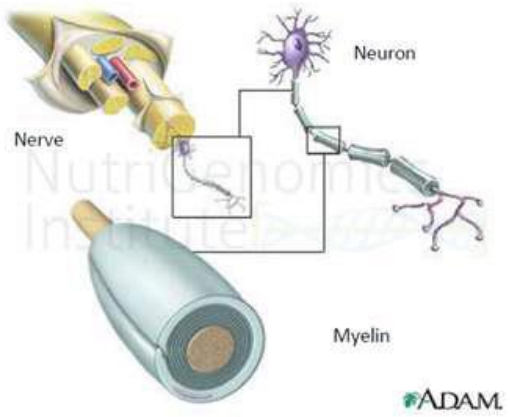
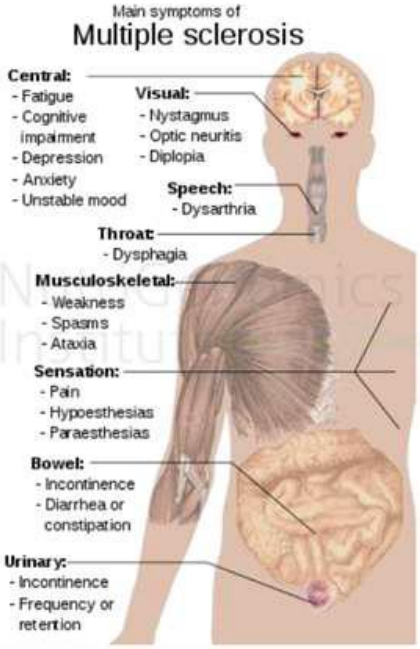
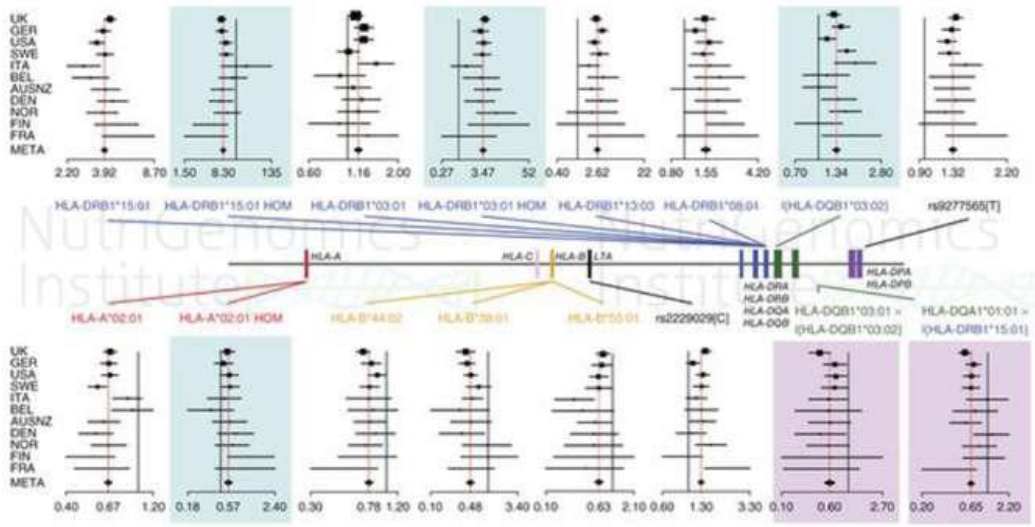




5. Nutrigenomics and Multiple Sclerosis (MS)



Nature Genetics 47, 1107–1113 (2015)

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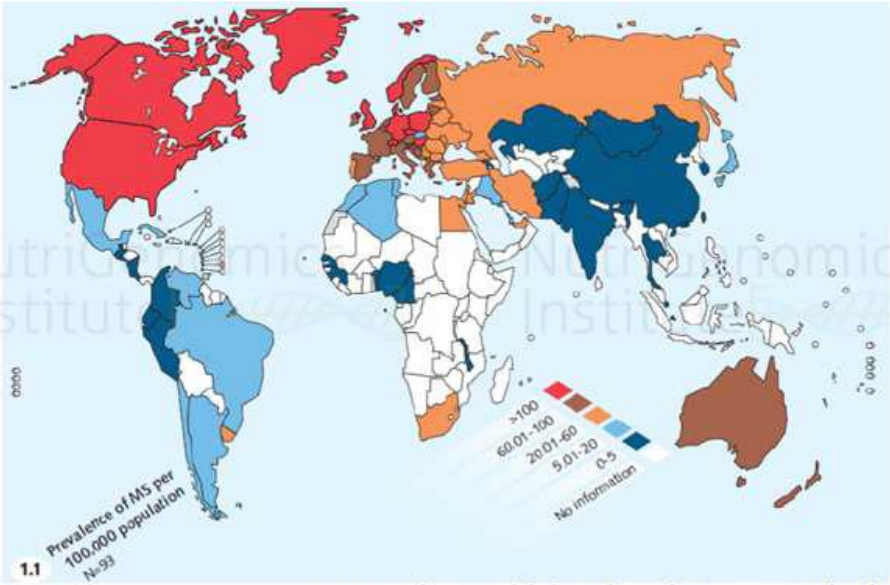

WHO Atlas: Multiple Sclerosis Resources in the World 2008

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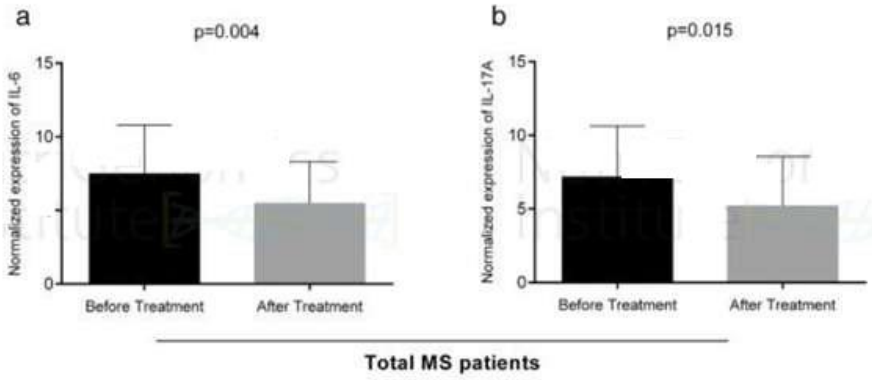

Int Immunopharmacol. 2015 Sep;28(1):414-9

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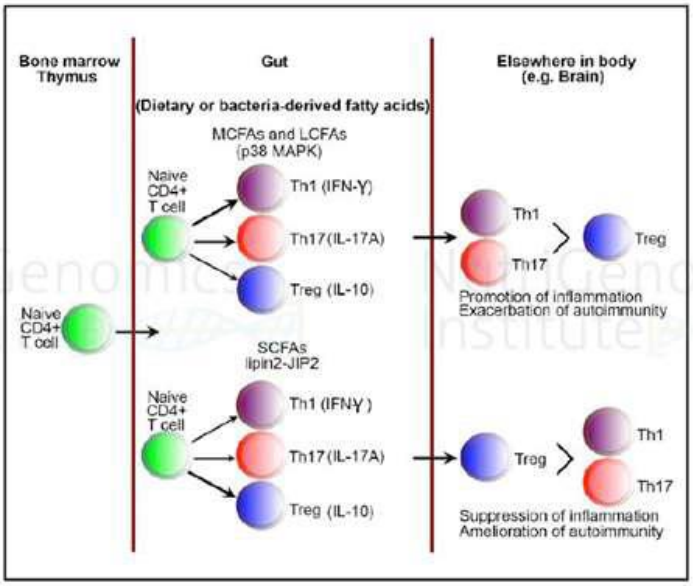


Immunity. 2015 Oct 20;43(4):817-29 y Nat Rev Immunol. 2015 Dec;15(12):726-7

Nutrigenomics and longevity.

Nutrigenomics and longevity.

1. Molecular basis of aging.
2. Caloric restriction and modification of gene expression.
3. Mitochondrial genomics and aging.

Nutrigenomics and longevity.

Nutrigenomics and longevity.

Chronological age and biological age. Frailty. Aging phenotypes.

Nutrigenomics and longevity.

Exposure and response to damage. Resilience.

Nutrigenomics and longevity.

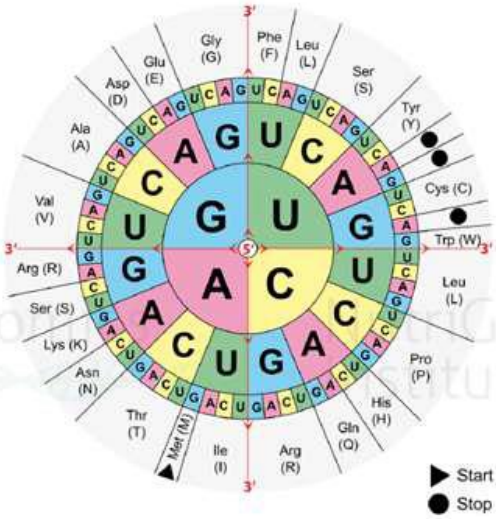
$$\mathrm{BA}_i = \mathrm{Predicted\,CA}_i = a_0 + \sum_{j=1}^{m} b_j x_{ji}.$$

Exposure, traits, repair.

Nutrigenomics and longevity.

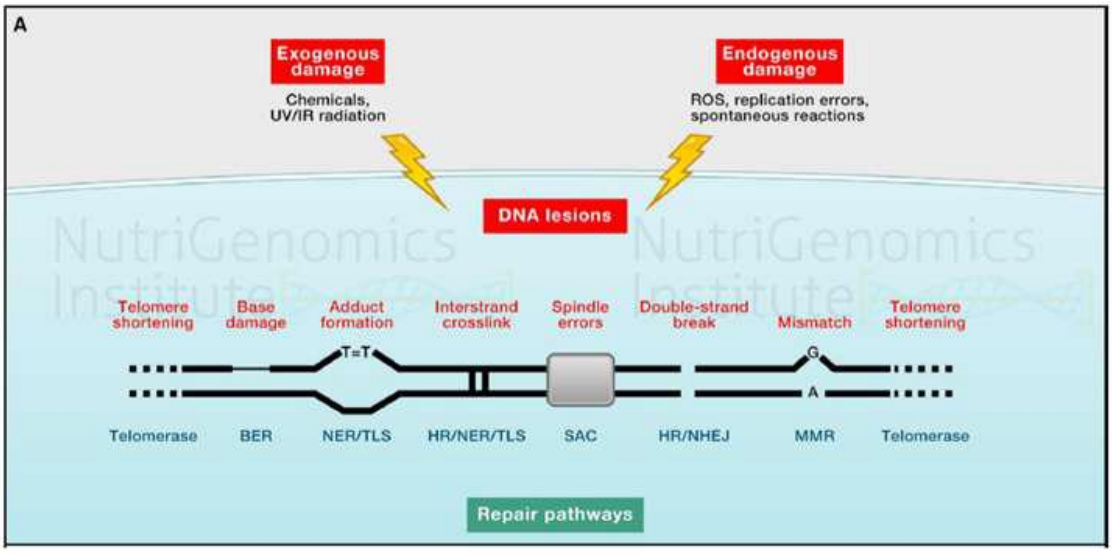
Chance. Damage accumulation. The free radical theory of aging (FRTA).

Nutrigenomics and longevity.



Chance. Damage accumulation. The free radical theory of aging (FRTA).

Nutrigenomics and longevity.



Cell 2013 153, 1194-1217

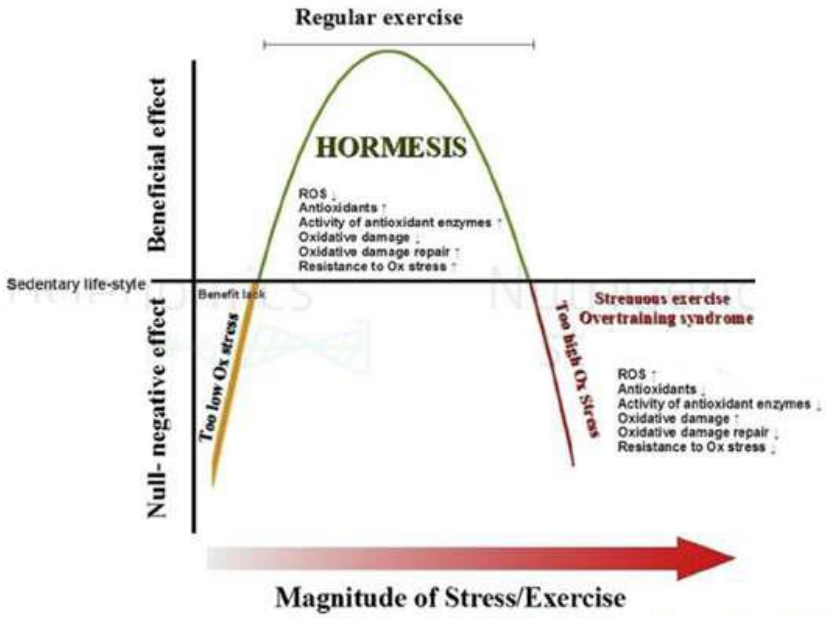
Nutrigenomics and longevity.

Cell 2013 153, 1194-1217

Nutrigenomics and longevity.

Food and Nutrition

Nutrigenomics and longevity.



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Nutrigenomics and longevity.

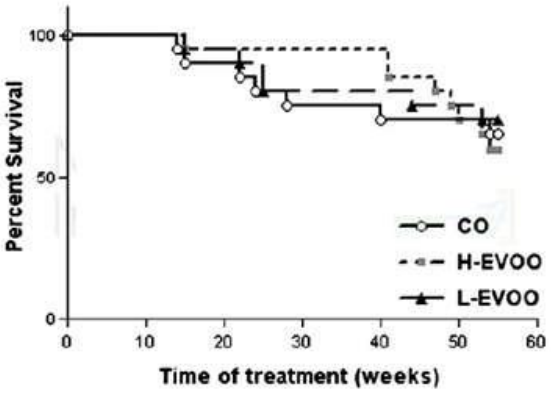


Table 3
Blood oxidative damage-related parameters

	CO	H-EVOO	L-EVOO
DNA strand breaks (%DNA in tail)	6.33±0.40	5.75±0.44	6.08±0.47
DNA FPG sites (%DNA in tail)	16.06±1.70	13.59±1.47*	19.83±1.40
plasma TBARS (μmol/ml)	3.12±0.64	1.61±0.30*,#	2.95±0.55

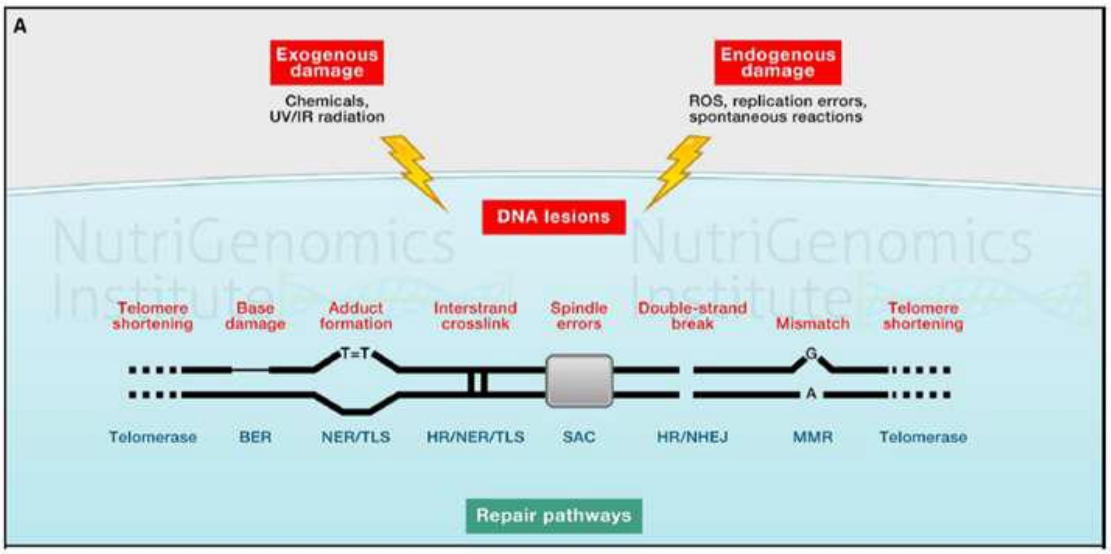
CO, corn oil; H-EVOO, extra-virgin olive oil rich in natural antioxidants; L-EVOO, extra-virgin olive oil poor in natural antioxidants. Values are expressed as mean±S.E.M. ($n=11-13$). Leukocyte DNA strand breaks and FPG sites were measured with the comet assay.

# $P<.05$ vs. CO.

* $P<.05$ vs. L-EVOO.

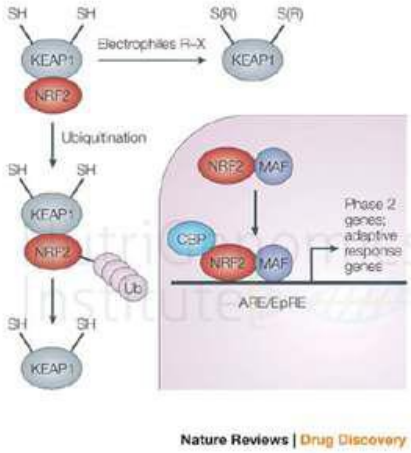
Cell 2013 153, 1194-1217

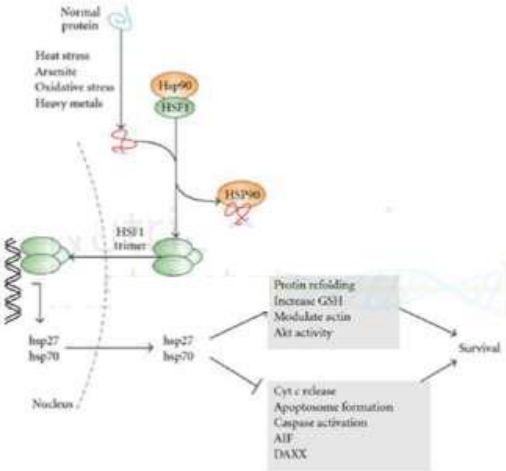
Nutrigenomics and longevity.



Cell 2013 153, 1194-1217

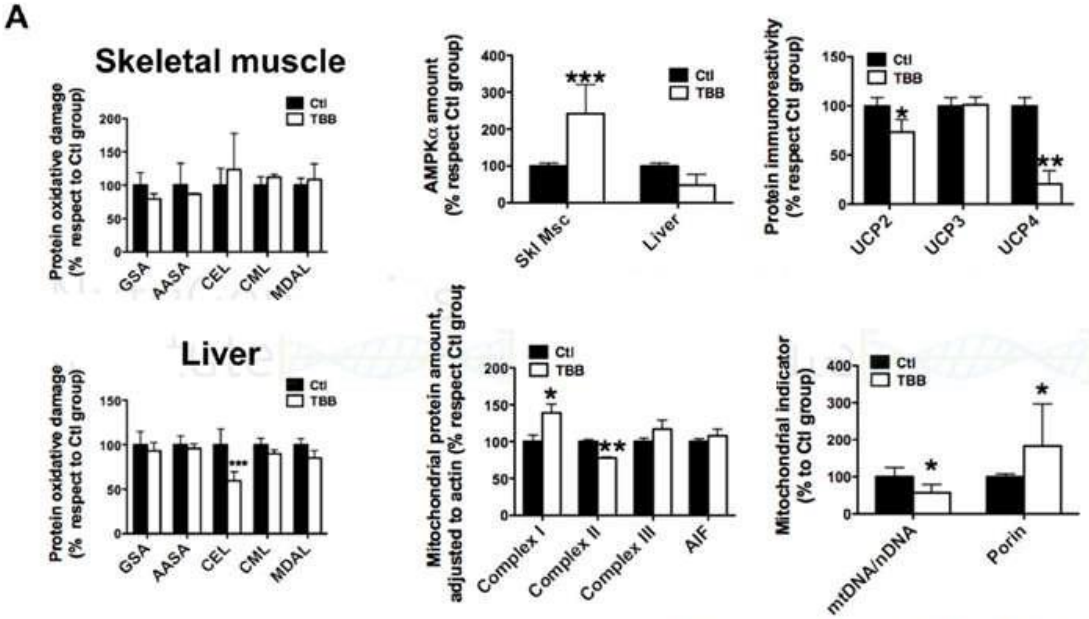
Nutrigenomics and longevity.





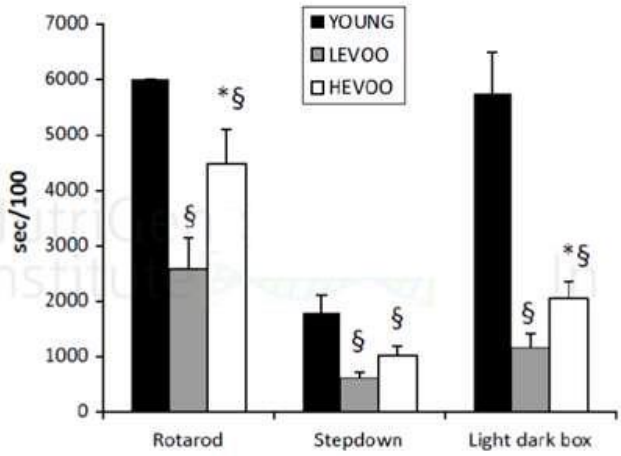
Nature Reviews Drug Discovery 4, 410-420 (May 2005) y IJCB Vol 2010 (2010), Article ID 214074

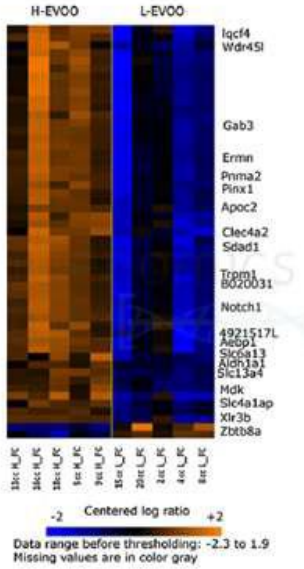
Nutrigenomics and longevity.



Mol Nutr Food Res. 2013 Mar;57(3):459-70

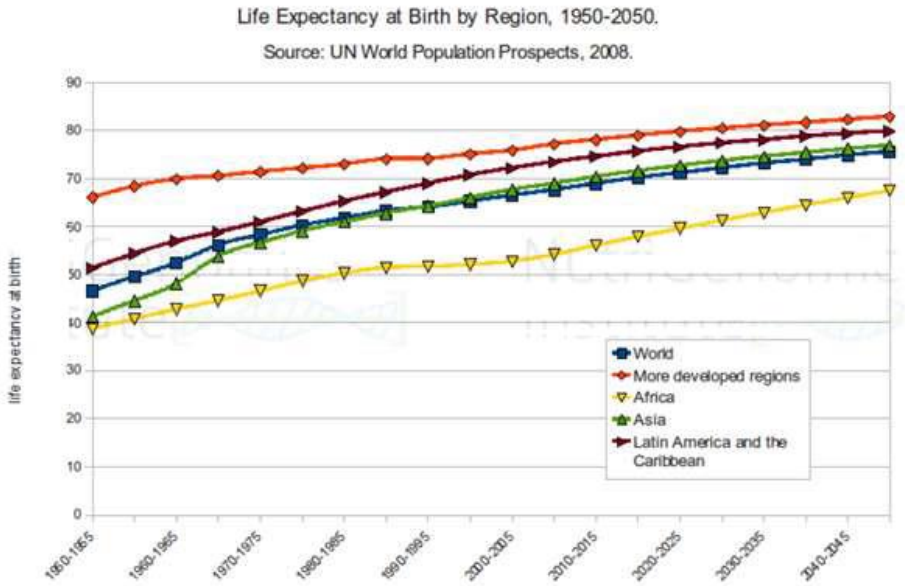
Nutrigenomics and longevity.



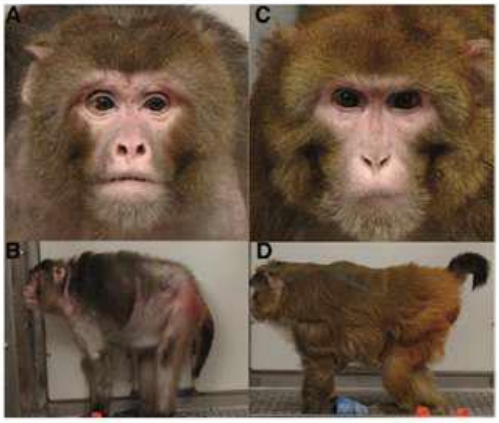


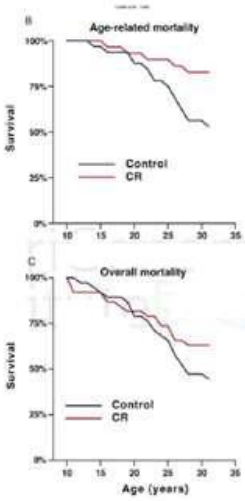
British Journal of Nutrition (2010), 103, 1674–1683

Nutrigenomics and longevity.



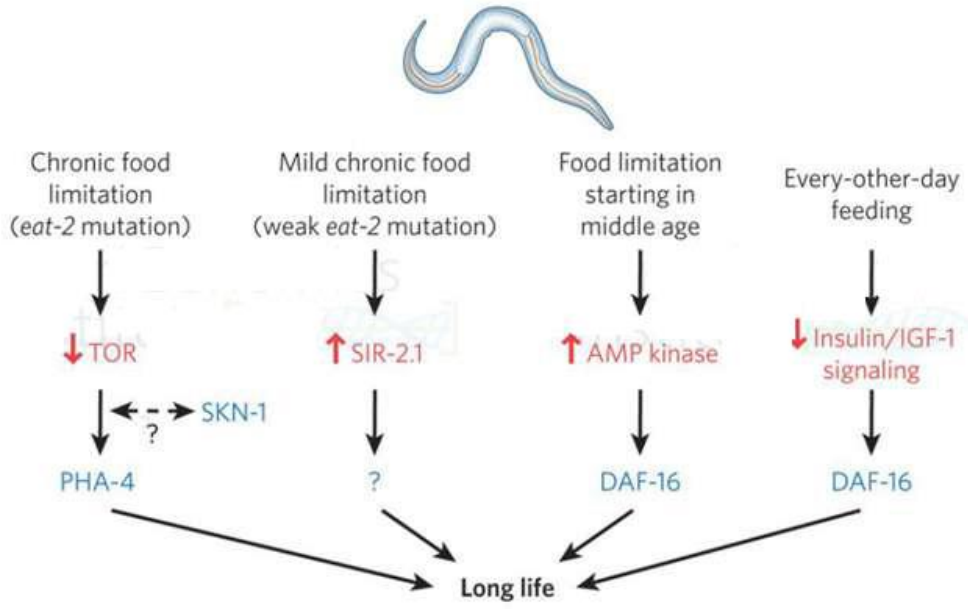
Nutrigenomics and longevity.





Science. 2009 Jul 10;325(5937):201-4

Nutrigenomics and longevity.



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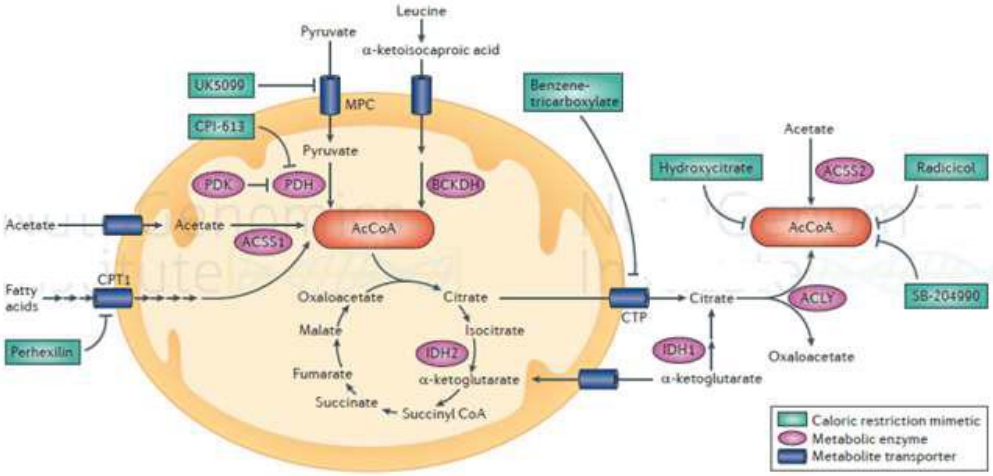
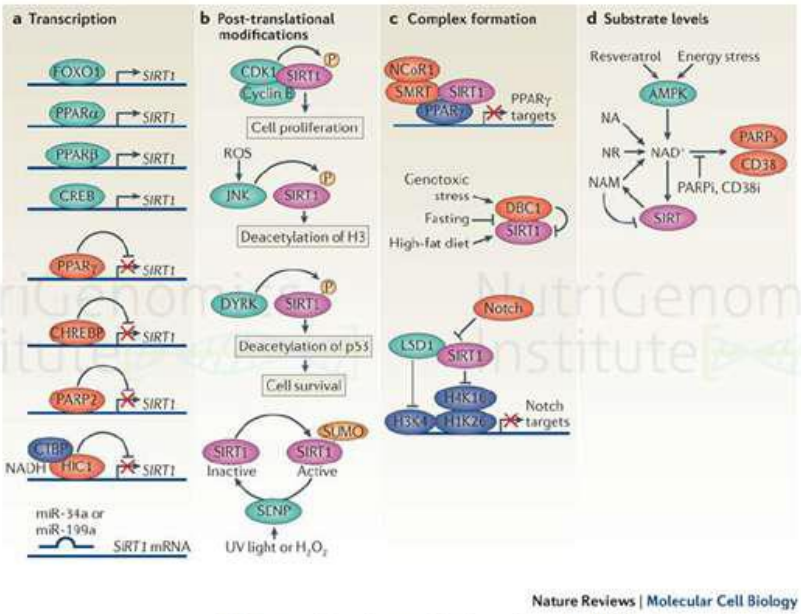


Nature Reviews Drug Discovery 13, 727–740 (2014)

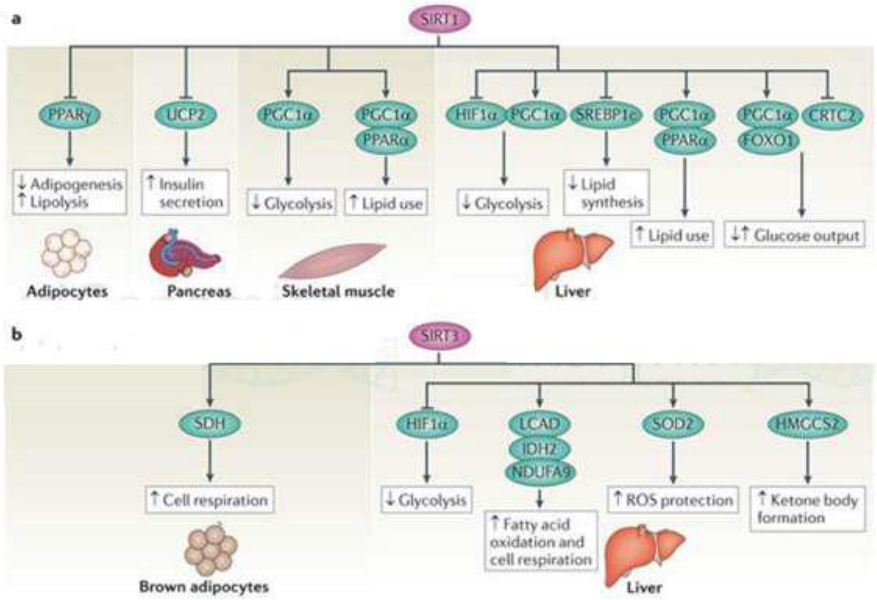
Nutrigenomics and longevity.



Nature Reviews | Molecular Cell Biology

Nature Reviews Molecular Cell Biology 13, 225-238 (April 2012)

Nutrigenomics and longevity.



Nature Reviews Molecular Cell Biology 13, 225-238 (April 2012)

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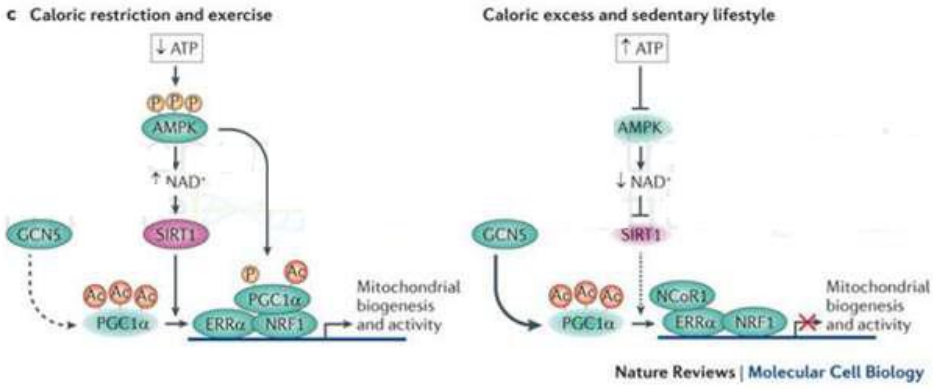

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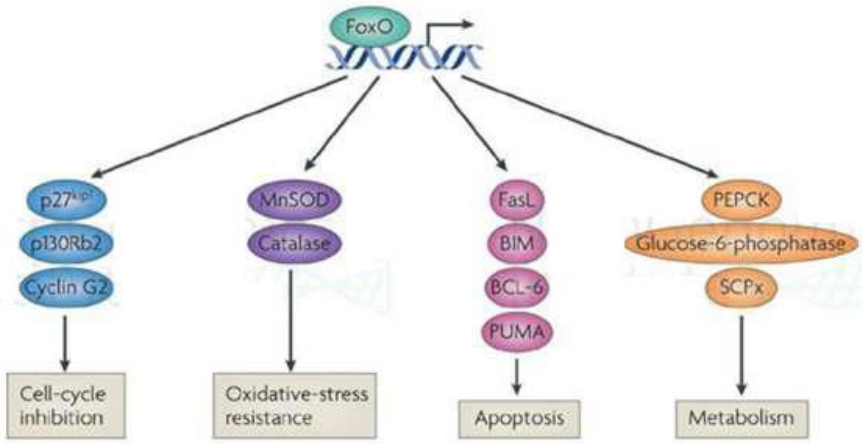

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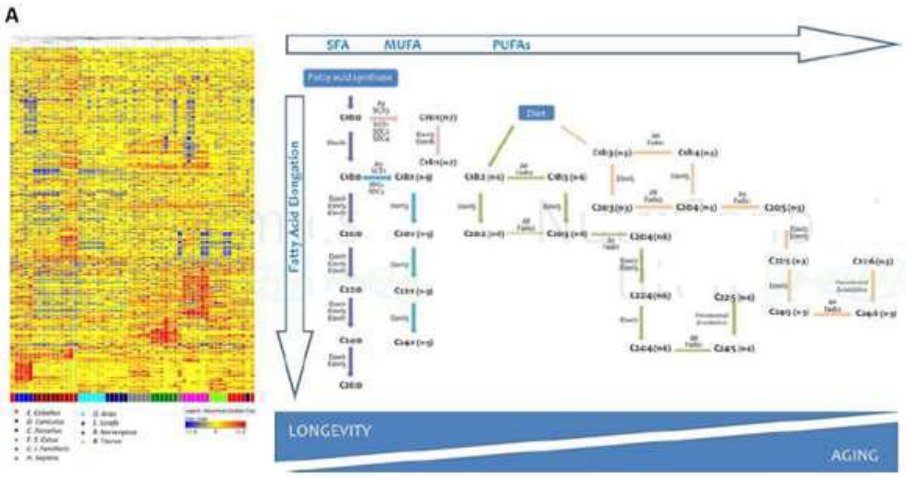
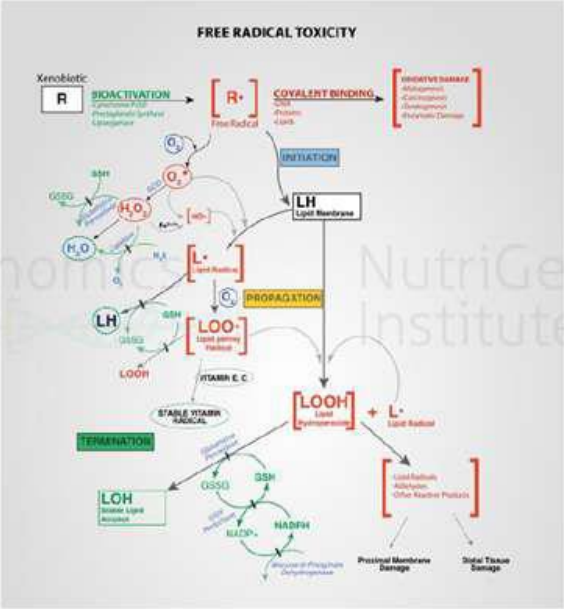
Nature Reviews Molecular Cell Biology 8, 440-450 (June 2007)

Nutrigenomics and longevity.

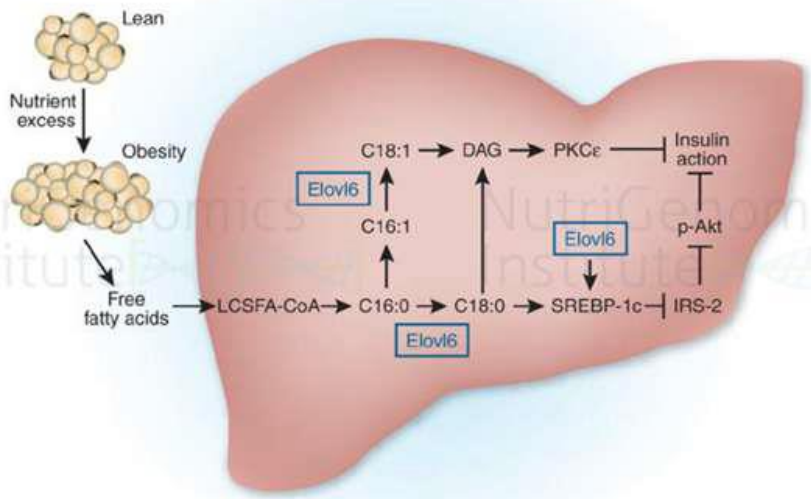


Scientific Reports **3**, Article number: 3346 (2013) y Front Physiol. 2013; 4: 372.

Nutrigenomics and longevity.

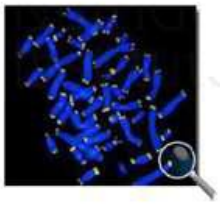


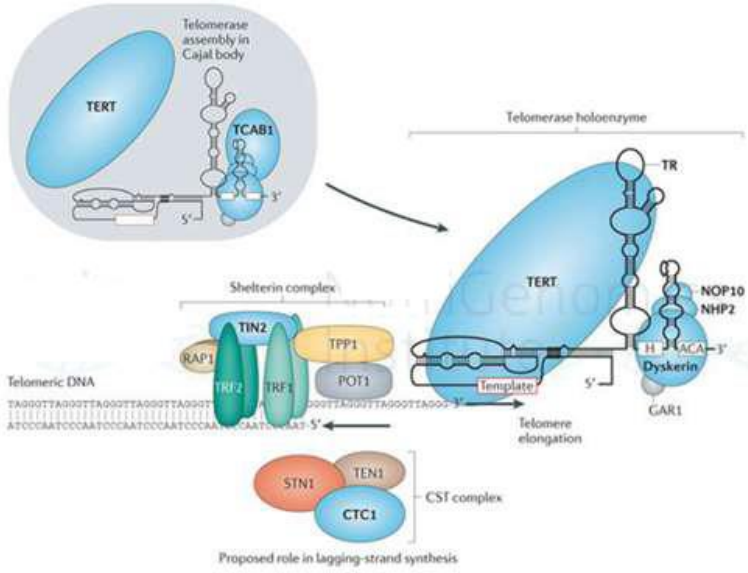
Nutrigenomics and longevity.



Nature Medicine 13, 1137 - 1138 (2007)

Nutrigenomics and longevity.

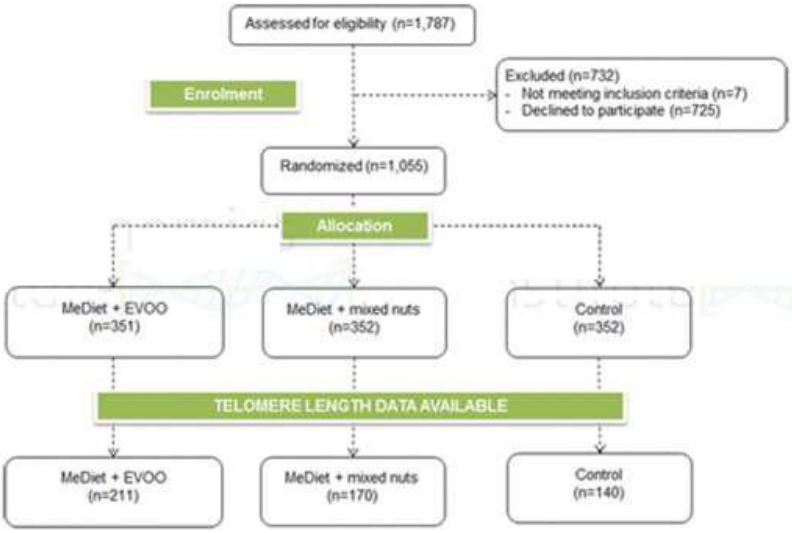




Nature Reviews | Genetics

Cell 2013 153, 1194-1217

Nutrigenomics and longevity.



Circulation: Cardiovascular Genetics. 2015; 8: 91-99

Nutrigenomics and longevity.

Table 4. Association between telomere length changes during follow-up and changes in anthropometric variables after 5 years of a nutritional intervention, according to tertiles of baseline TL in participants of the PREDIMED-NAVARRA trial

	Tertiles of baseline TL			*P for trend*
	T1	*T2*	*T3*	
Weight change (kg)				
Change in TL during follow-up				
TL decreased ($n = 314$)	0 (Ref.)	0.10 (−1.19 to 1.39)	−0.71 (−1.96 to 0.53)	0.197
TL increased ($n = 207$)	0.29 (−1.03 to 1.61)	−0.34 (−1.80 to 1.13)	−1.58 (−3.21 to 0.06)	0.008
BMI change (kg m^{-2})				
Change in TL during follow-up				
TL decreased ($n = 314$)	0 (Ref.)	−0.06 (−0.57 to 0.44)	−0.39 (−0.87 to 0.10)	0.111
TL increased ($n = 207$)	0.01 (−0.51 to 0.52)	−0.24 (−0.81 to 0.33)	−0.71 (−1.35 to −0.08)	0.009
Waist circumference change (cm)				
Change in TL during follow-up				
TL decreased ($n = 314$)	0 (Ref.)	0.68 (−0.89 to 2.25)	−0.88 (−2.41 to 0.64)	0.083
TL increased ($n = 207$)	−0.01 (−1.62 to 1.61)	−0.62 (−2.40 to 1.16)	−1.95 (−3.94 to 0.04)	0.044
Waist to height ratio change				
Change in TL during follow-up				
TL decreased ($n = 314$)	0 (Ref.)	0.003 (−0.007 to 0.013)	−0.007 (−0.016 to 0.003)	0.053
TL increased ($n = 207$)	−0.001 (−0.011 to 0.009)	−0.005 (−0.016 to 0.006)	−0.013 (−0.025 to 0.001)	0.051

Abbreviation: BMI, body mass index; TL, telomere length; The table shows B coefficients (95% CI). Adjusted for age, sex, basal BMI, basal WC, basal weight or WHtR, smoking (three categories), diabetes status (dichotomous), hypertensive status (dichotomous), dyslipidaemia status (dichotomous), physical activity (METs-min per day), total energy intake (Kcal per day) and group of intervention. T1 ⩽ 78.25; T2 = 78.25–198.08; T3 ⩾ 198.08.

Circulation: Cardiovascular Genetics. 2015; 8: 91-99

Nutrigenomics and longevity.

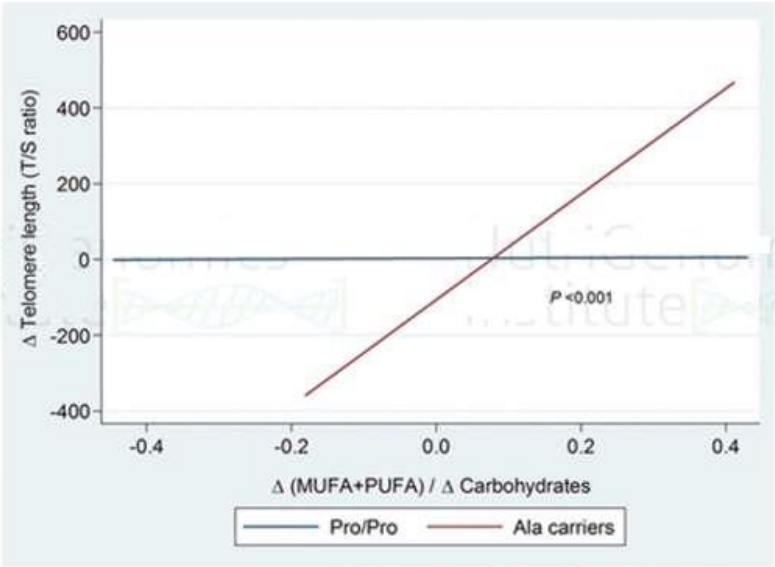
Table 5. Odds ratio and 95% CI of remaining obese (BMI $\geqslant 30$ kg m^{-2}) after 5 years of a nutritional intervention, according to tertiles of baseline TL and change in TL during follow-up

	Tertiles of baseline TL		
	T1	*T2*	*T3*
Change in TL during follow-up			
TL decreased ($n = 119$)	1 (Ref.)	0.50 (0.12–2.15)	0.43 (0.10–1.89)
TL increased ($n = 77$)	0.91 (0.19–4.42)	0.48 (0.10–2.31)	0.27 (0.03–2.03)

Abbreviations: BMI, body mass index; CI, confidence interval; TL, telomere length. Adjusted for age, sex, basal BMI, basal WC, smoking (three categories), diabetes status (dichotomous), hypertensive status (dichotomous), dyslipidaemia status (dichotomous), physical activity (METS-min per day), total energy intake (Kcal per day) and group of intervention. T1 $\leqslant$ 78.25; T2 = 78.25–198.08; T3 $\geqslant$ 198.08.

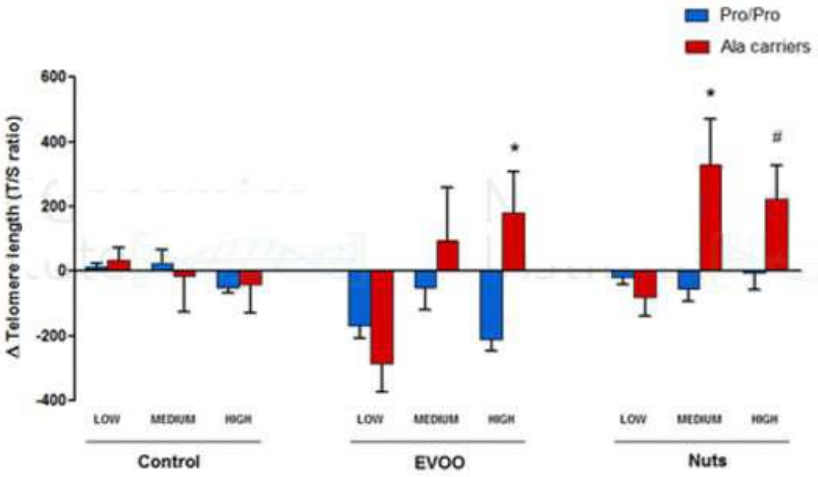
Circulation: Cardiovascular Genetics. 2015; 8: 91-99

Nutrigenomics and longevity.



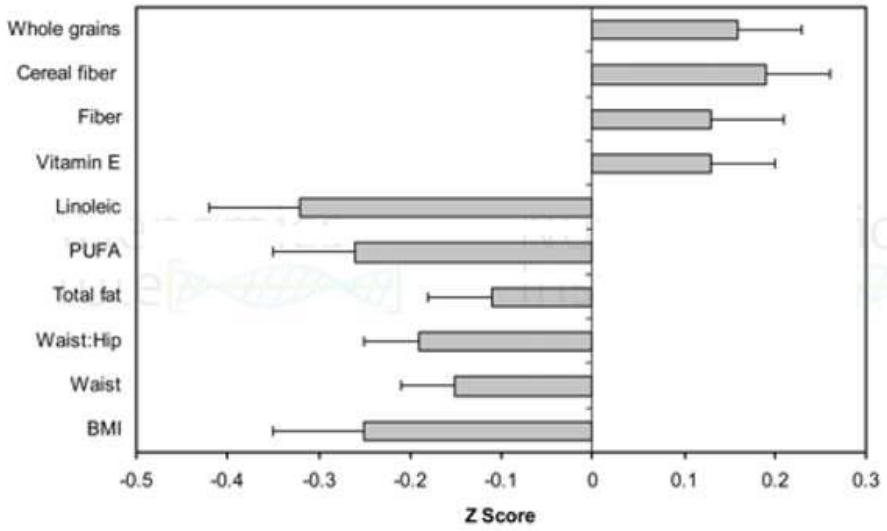
Circulation: Cardiovascular Genetics. 2015; 8: 91-99

Nutrigenomics and longevity.



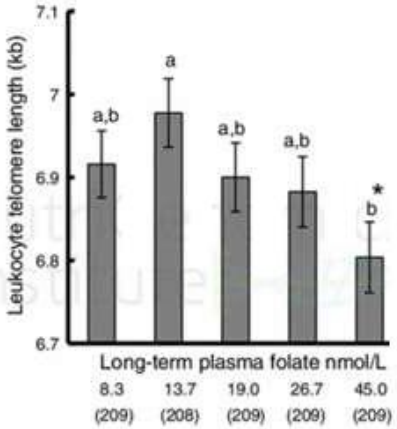
Circulation: Cardiovascular Genetics. 2015; 8: 91-99

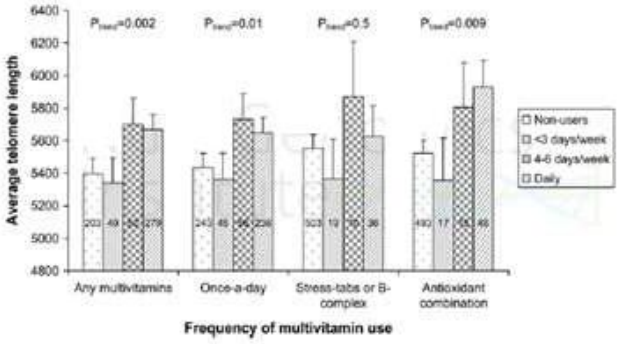
Nutrigenomics and longevity.



Am J Clin Nutr May 1, 2010 vol. 91 no. 5 1273-1280

rigenomics and longevity.





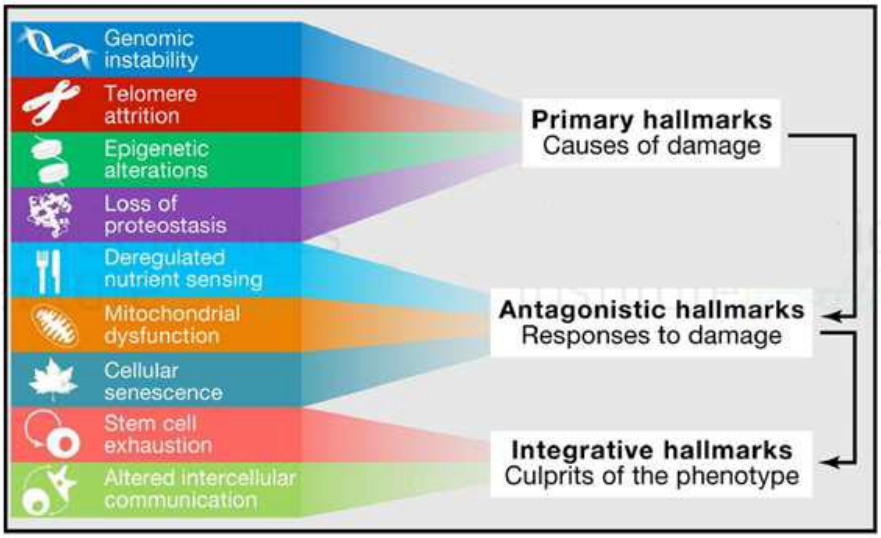
ı 2015, Volume 54, Issue 2, pp 235–241 y J Clin Nutr June 2009 vol. 89 no. 6 1857-1863

Nutrigenomics and longevity.

Variables	Model 1 β	Model 2 β	Model 3 β
Individual micronutrient z-scores			
Lutein and zeaxanthin	0.079	0.107	0.120
β-cryptoxanthin	0.060	0.041	0.040
Canthaxanthin	0.018	0.049	0.056
Lycopene	−0.080	−0.064	−0.069
α-carotene	−0.027	−0.020	-0.028
β-carotene	−0.069	−0.065	-0.077
α-tocopherol	−0.012	0.013	0.019
γ-tocopherol	−0.002	0.041	0.044
Vitamin C	0.160	0.152	0.14
Retinol	−0.055	−0.065	−0.058

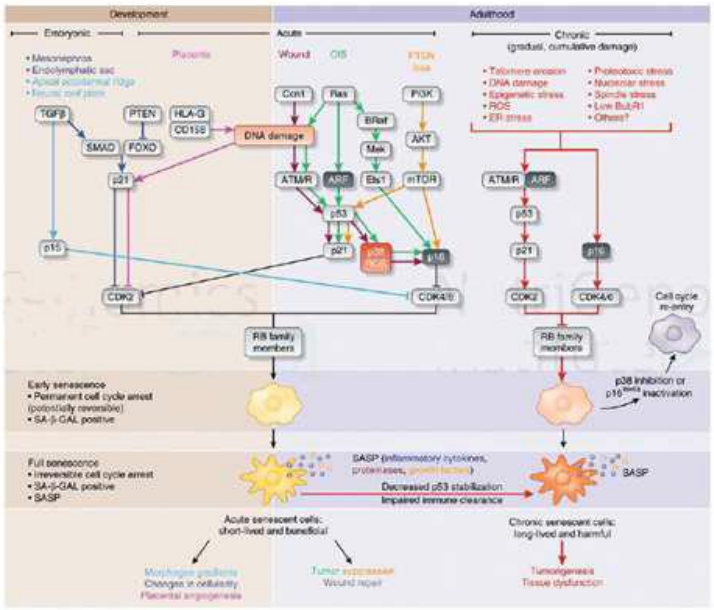
JAGS Volume 62, Issue 2 February 2014 Pages 222–229

Nutrigenomics and longevity.



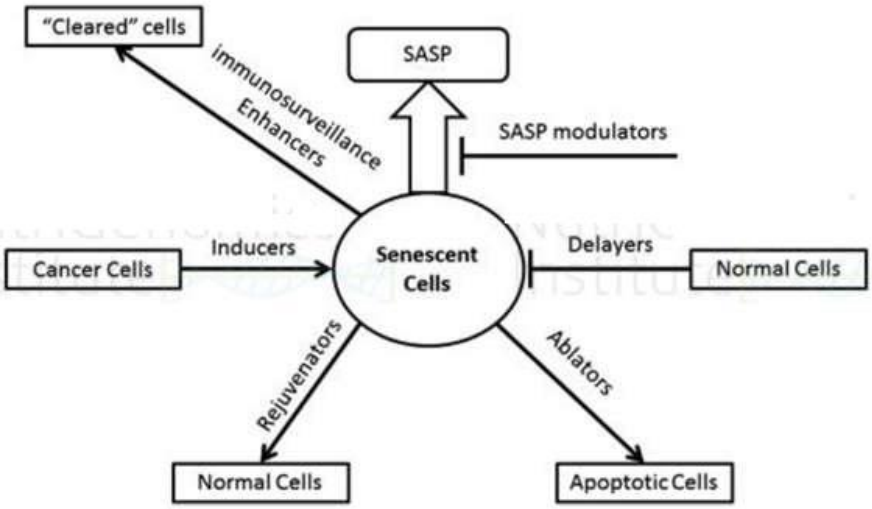
Cell 2013 153, 1194-1217

Nutrigenomics and longevity.



Nature Medicine 21, 1424–1435 (2015)

Nutrigenomics and longevity.

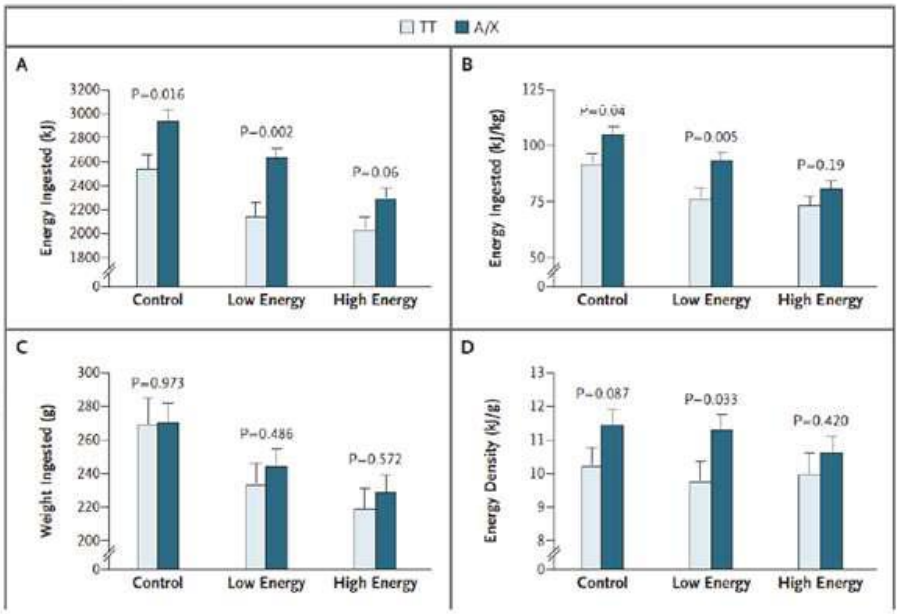


Nature Medicine 21, 1424–1435 (2015)

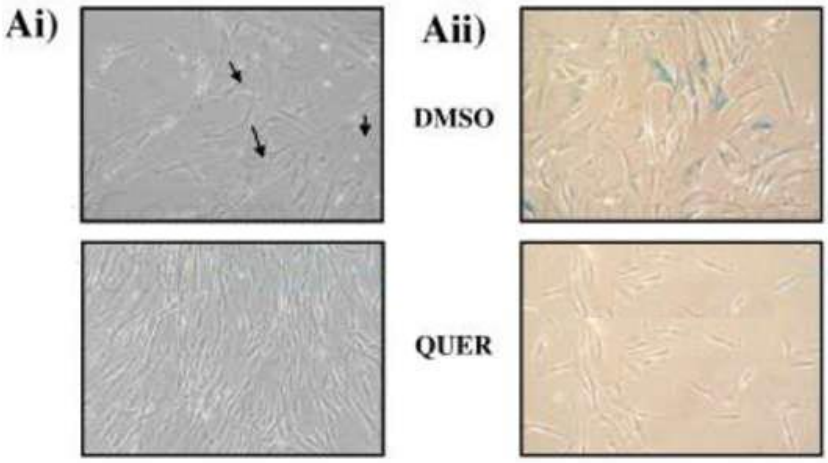
An obesity-associated FTO gene variant and increased energy intake in children
(Cecil, 2008)
N Engl J Med 359:2558-2566

FTO rs9939609

	BMI
TT (n=1016)	17,09
AT (n=1322)	17,17
AA (n=388)	17,58
Signif.	p=0,003

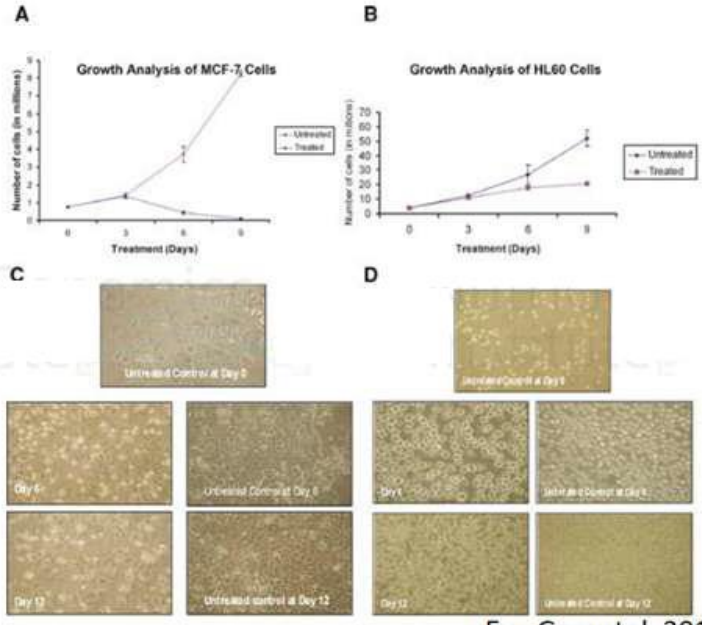


Nutrigenomics and longevity.



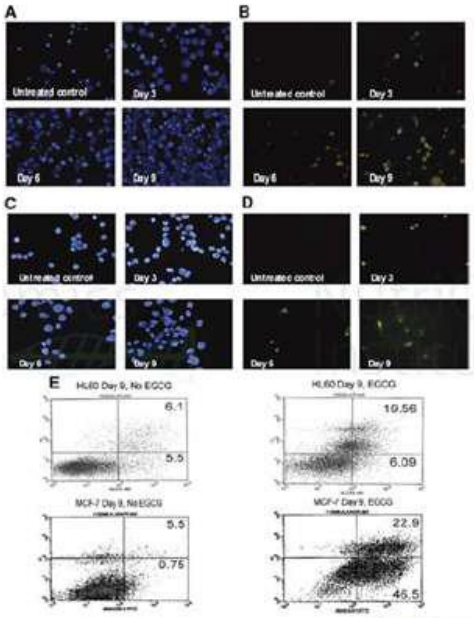
Exp Gerontol. 2010 Oct;45(10):763-71

Nutrigenomics and longevity.



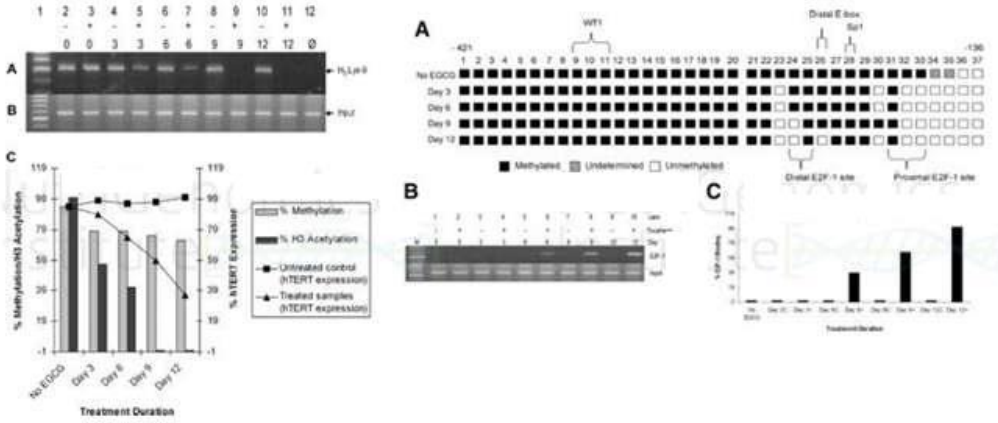
Exp Gerontol. 2010 Oct;45(10):763-71

Nutrigenomics and longevity.



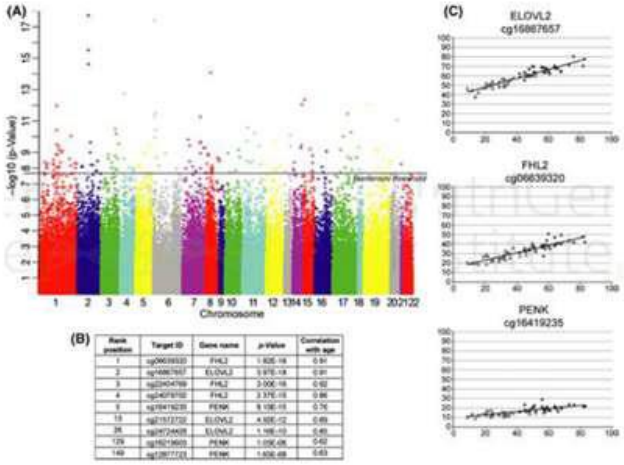
Exp Gerontol. 2010 Oct;45(10):763-71

Nutrigenomics and longevity.



Exp Gerontol. 2010 Oct;45(10):763-71

Nutrigenomics and longevity.

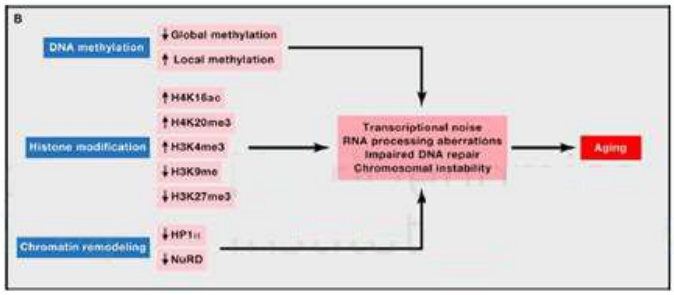


Aging Cell. 2012 Dec;11(6):1132-4.

Nutrigenomics and longevity.

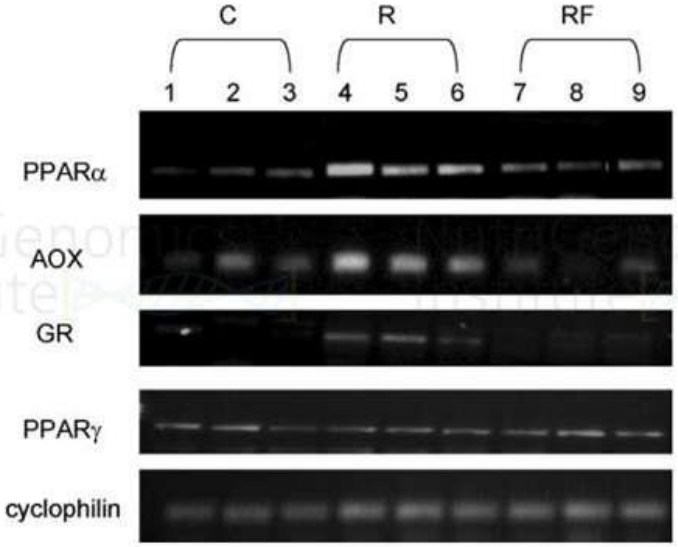
- Components and dietary practices with epigenetic actions

- Methylation
  - Folate and Choline
  - Isoflavones: genisteine
  - Zinc
  - Selenium
  - Vitamine A
  - Protein restriction
- Histone modification
  - Butyrate
  - Isothiocyanates
  - Folate and choline
  - Retinoic acid
  - Protein restriction
- Non-coding RNAs
  - Zinc
  - Vitamine D



Cell 2013 153, 1194-1217

Nutrigenomics and longevity.



J Nutr. 2005 Jun;135(6):1382-6.

Nutrigenomics and longevity.

Br J Nutr. 2007 Mar; 97(3): 435–439.

Nutrigenomics and longevity.

Index

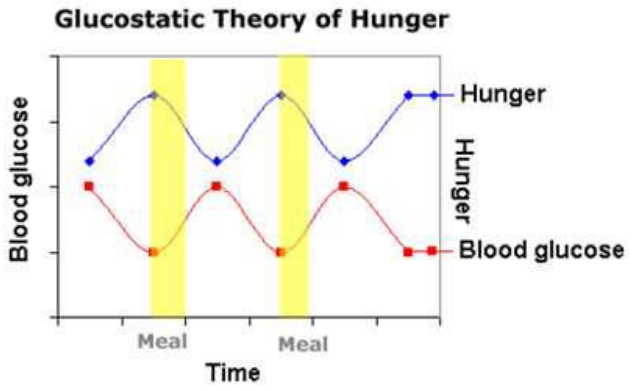
Understanding Satiety, what is its role?

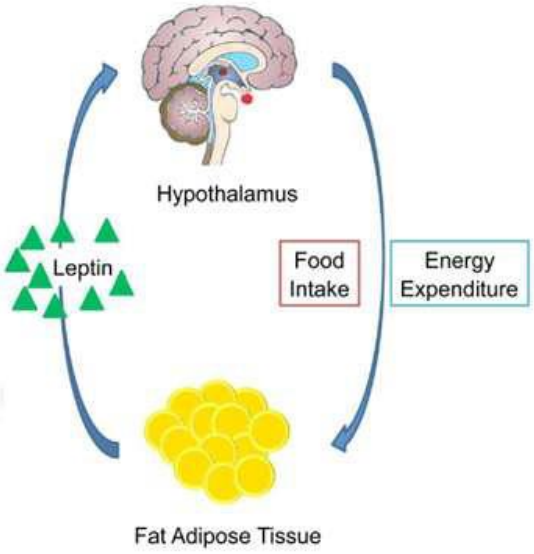
1. Better use of nutrients
    - Regulation of motility
    - Regulation of secretion
    - Restriction of the amount of nutrients that reach the gastrointestinal tract (GIT), thus enhancing absorption
    - Avoidance of overconsumption adverse effects

- Avoidance of high blood glucose levels (glycemic-hypothalamus control)

- Avoidance of overstorage of nutrients (adipose tissue control, leptin, adiponectin)
    - Insulin-resistance
    - Adypocite hypertrophy

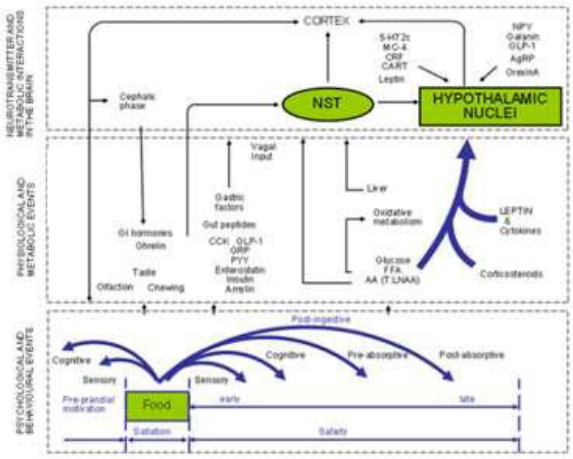
REGULATION OF ENERGY INTAKE AND THE BODY WEIGHT: THE GLUCOSTATIC THEORY AND THE LIPOSTATIC HYPOTHESIS
Jean Mayer, 1955

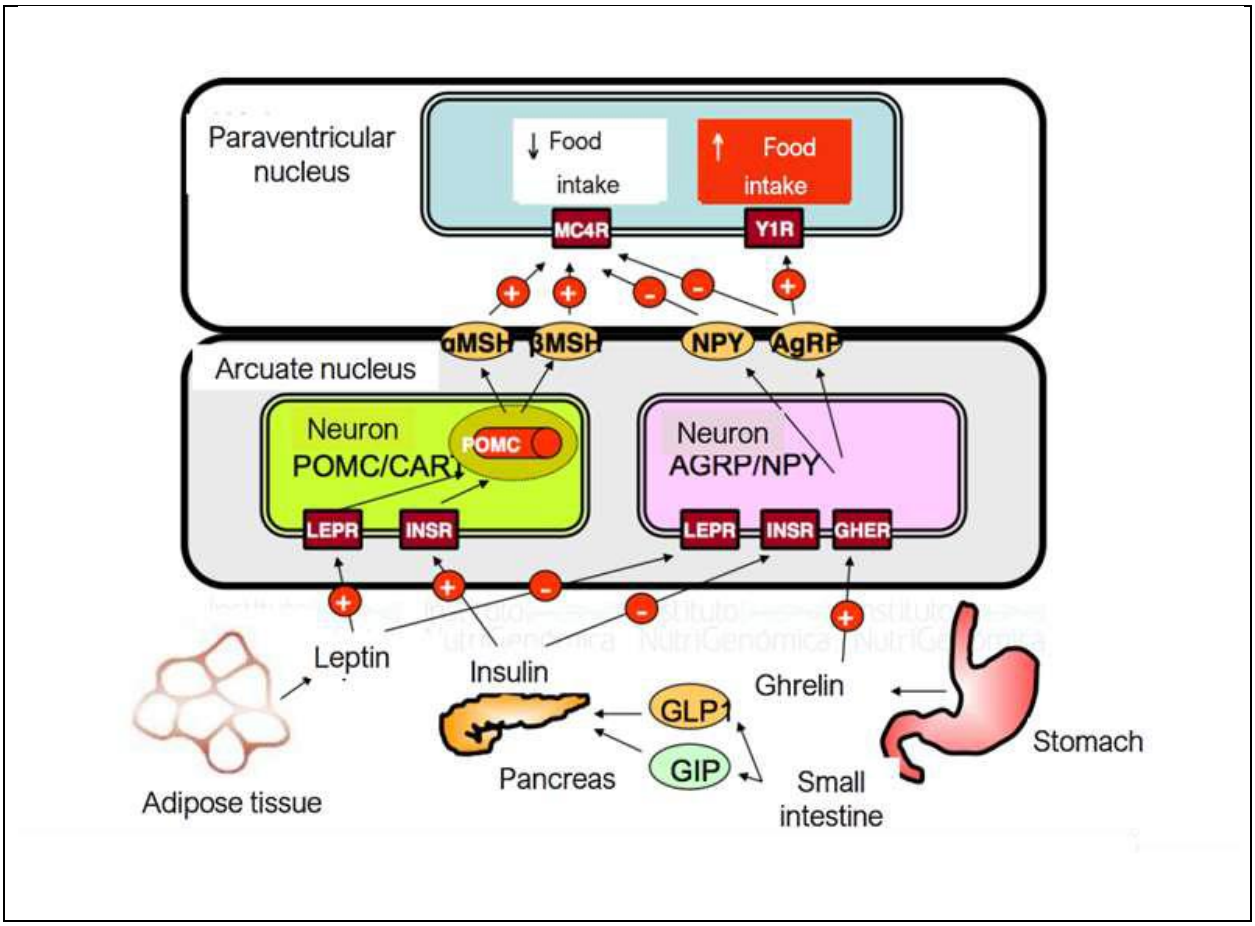




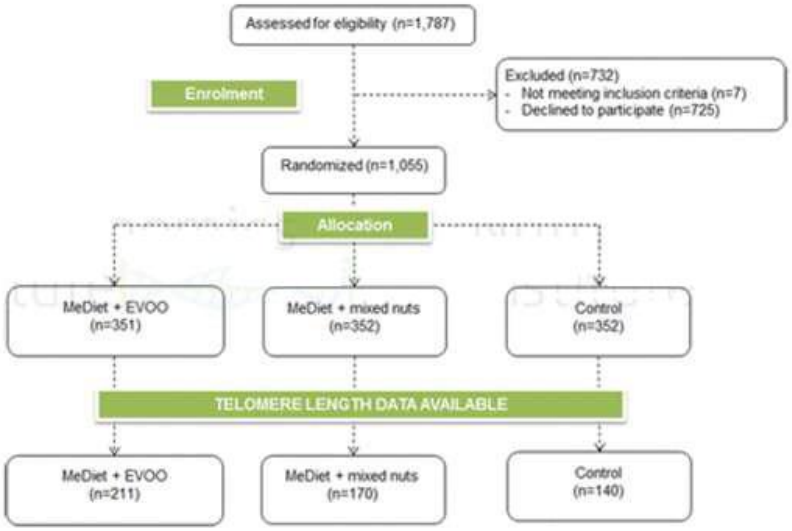
Satiation: processes that prompt the termination of food intake

Satiety: postprandial processes that affect the time of appearance of hunger or the start of a new phase of food intake




Paraventricular nucleus
↓ Food intake
↑ Food intake
MC4R
Y1R
αMSH
βMSH
NPY
AgRP
Arcuate nucleus
Neuron POMC/CART
POMC
Neuron AGRP/NPY
LEPR
INSR
LEPR
INSR
GHER
Leptin
Insulin
Ghrelin
GLP1
GIP
Pancreas
Small intestine
Stomach
Adipose tissue

Nutrigenomics and longevity.



Circulation: Cardiovascular Genetics. 2015; 8: 91-99

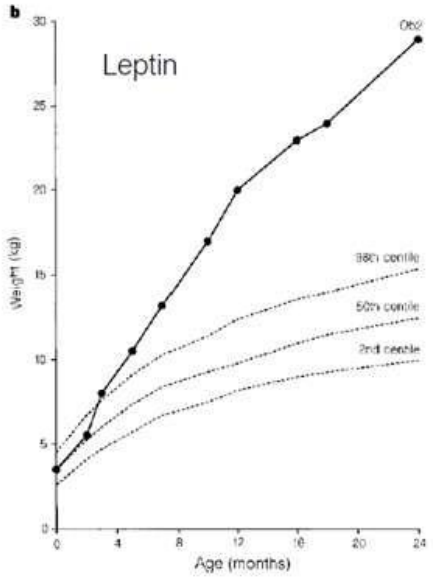
Index

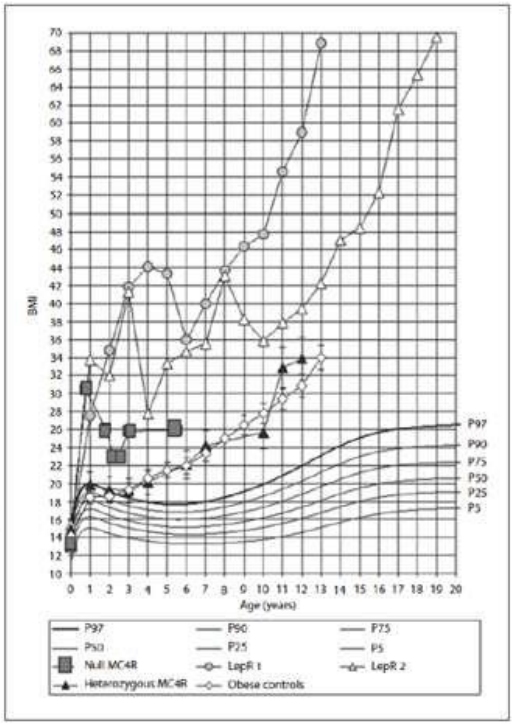
Rare genetic forms of obesity: Clinical approach and current treatments in 2016
(Huvenne et al, 2016)
Obes Facts 2016;9:158-176

Gene	Mutation type	Prevalence	Obesity
Leptin	Homozygous mutation	Diagnosed in fewer than 100 patients worldwide	Severe, from the first days of life
LEPR	Homozygous mutation	2-3% of patients with severe early-onset obesity	Severe, from the first days of life
POMC	Homozygous or compound heterozygous	Diagnosed in fewer than 10 patients worldwide	Severe, from the first months of life
PCSK1	Homozygous or compound heterozygous	Diagnosed in fewer than 20 patients worldwide	Severe obesity occurring in childhood
SIM1	Translocation between car 1p22.1 and 6q16.2 in the *SIM1* gene	Diagnosed in fewer than 50 patients worldwide	Severe obesity occurring in childhood
NTRK2	De novo heterozygous mutation	Diagnosed in fewer than 10 patients worldwide	Severe obesity from the first months of life

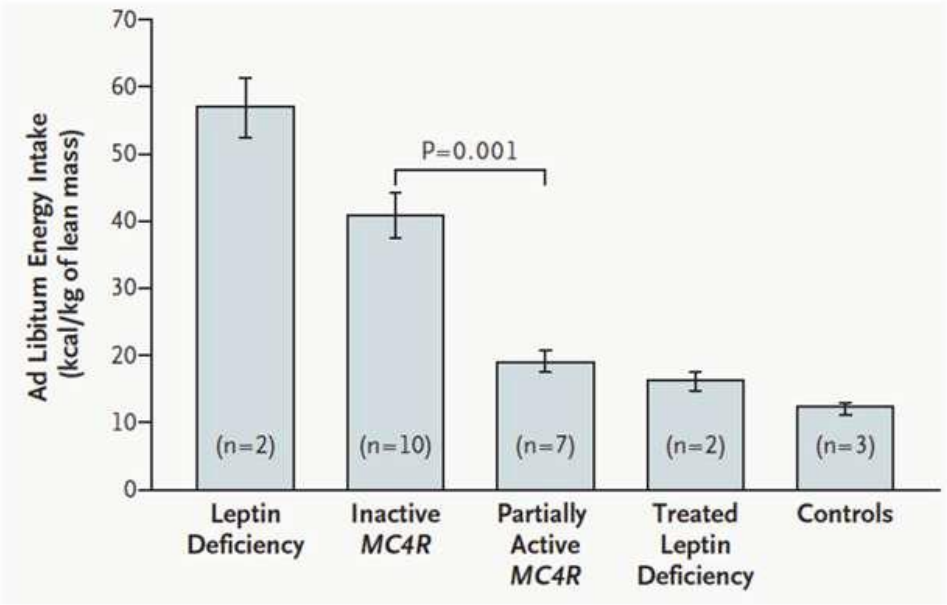
Congenital leptin deficiency is associated with severe early-onset obesity in humans

(Montague et al, 1997)
Nature, Vol 387, 903-908

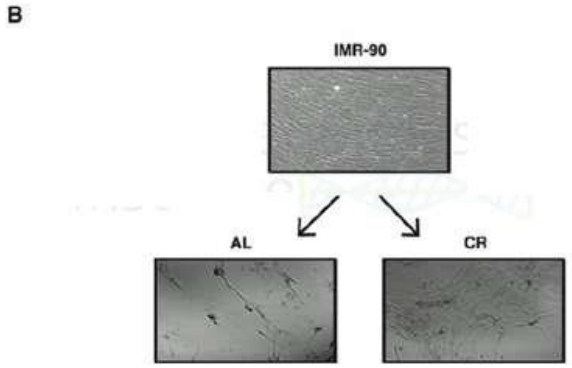


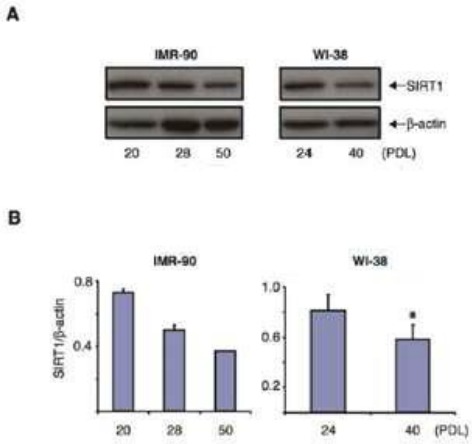


Effect of deficiencies in Satiety Mechanisms on energy intake



Nutrigenomics and longevity.



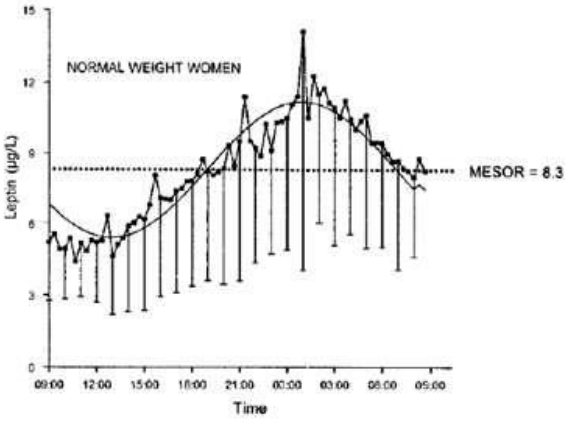


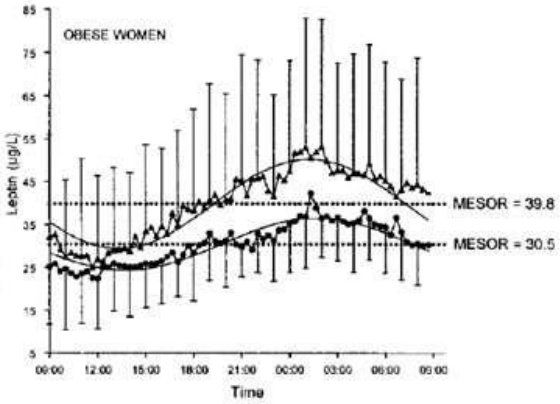
Aging (Albany NY). 2015 Mar;7(3):152-66.

Circadian rhythm of plasma leptin levels in upper and lower body obese women: influence of body fat distribution and weight loss

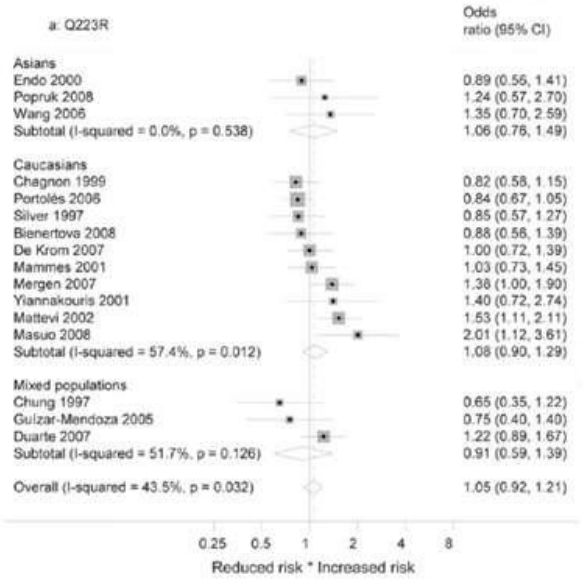
(Langendonk et al, 1998)

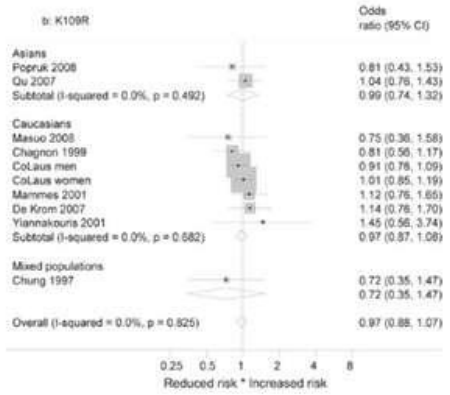
J Clin Endocrinol Metab 83:1706-1712

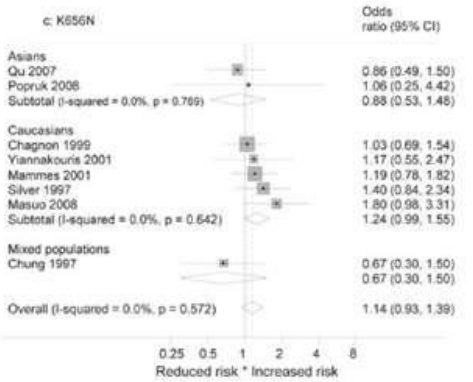




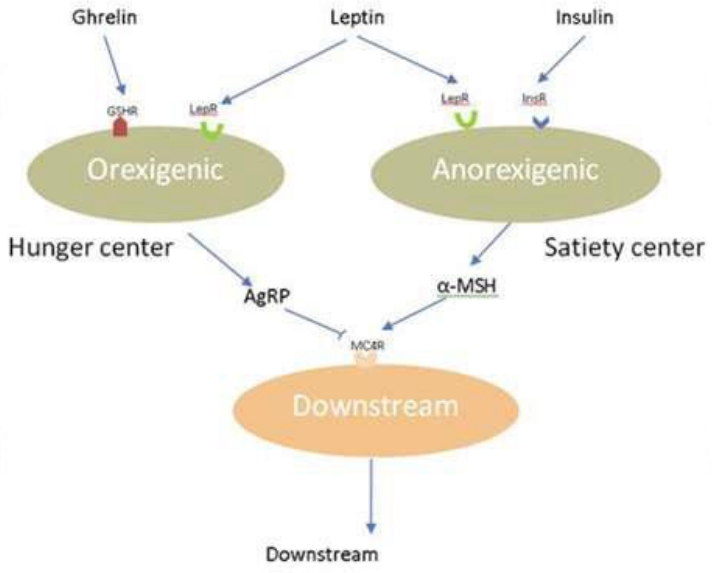
Association between variants of the Leptin Receptor Gene (LEPR) and overweight: A systematic review and meta-analysis



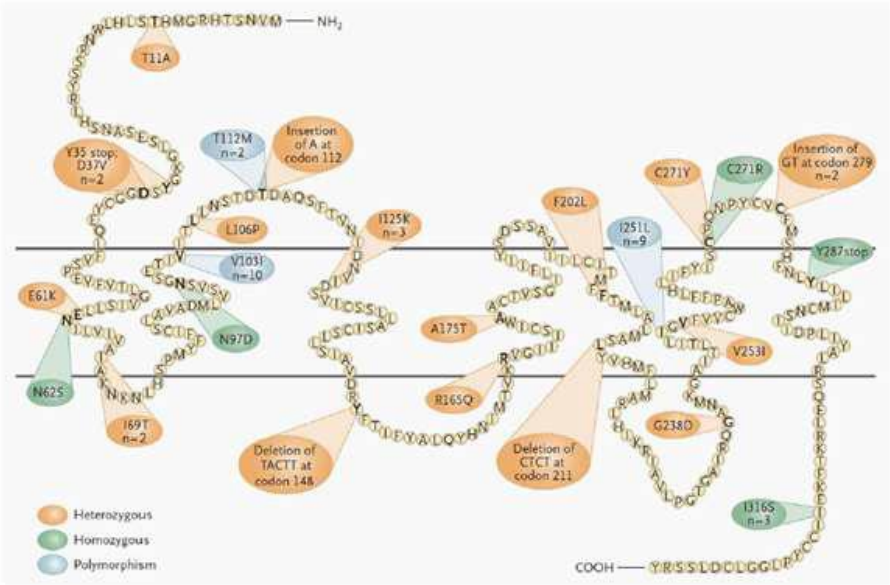


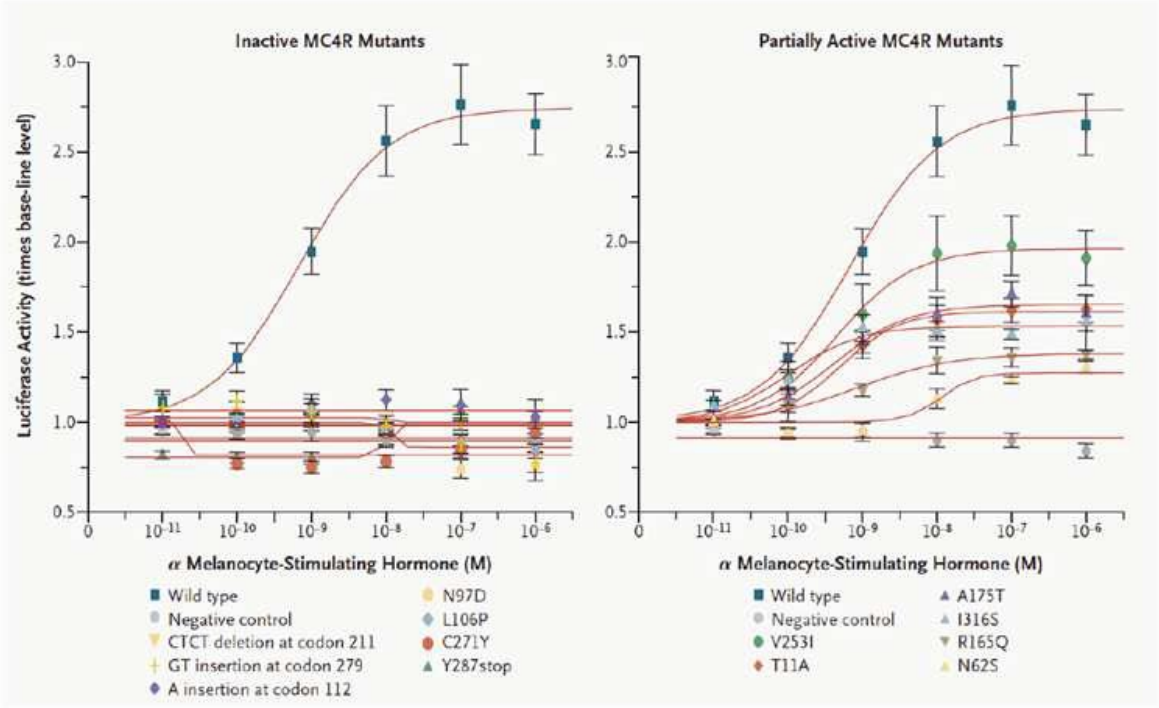


Physiology of Melanocortin-4 Receptor (MC4R)

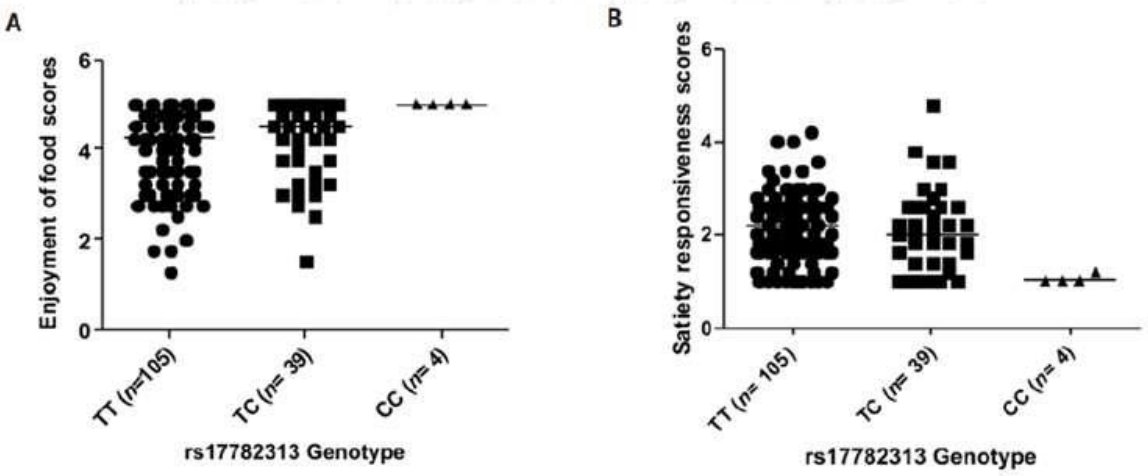


Melanocortin-4 receptor (*MC4R*) gene variants

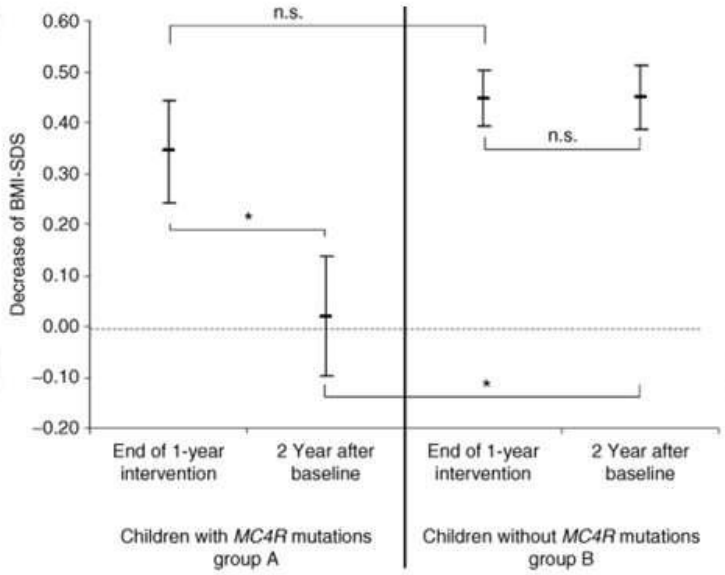



Inactive MC4R Mutants
Partially Active MC4R Mutants
Luciferase Activity (times base-line level)
3.0
2.5
2.0
1.5
1.0
0.5
0
10-11
10-10
10-9
10-8
10-7
10-6
α Melanocyte-Stimulating Hormone (M)
Wild type
Negative control
CTCT deletion at codon 211
GT insertion at codon 279
A insertion at codon 112
N97D
L106P
C271Y
Y287stop
Wild type
Negative control
V253I
T11A
A175T
I316S
R165Q
N62S

Melanocortin-4 receptor gene variants in Chilean families: association with childhood obesity and eating behavior
(Valladares et al, 2010)
Nutritional Neuroscience 13:71-78



Lifestyle intervention in obese children with variations in the melanocortin-4 receptor gene.
(Reinehr et al, 2009)
Obesity 17:382-389



Five year outcome of bariatric surgery in a patient with melanocortin-4 receptor mutation
(Elkhenini et al, 2014)
Clinical obesity, 4:121-124

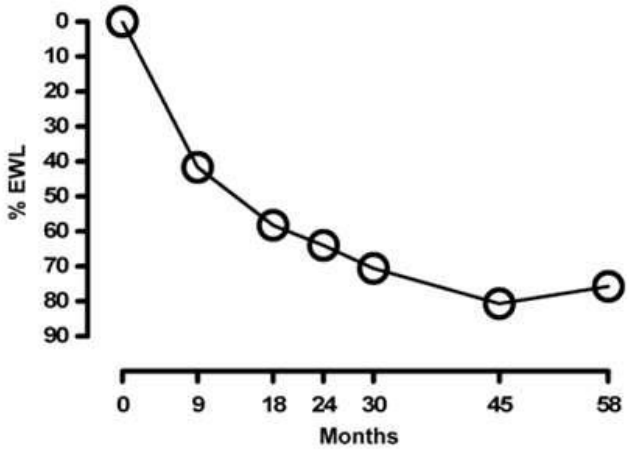
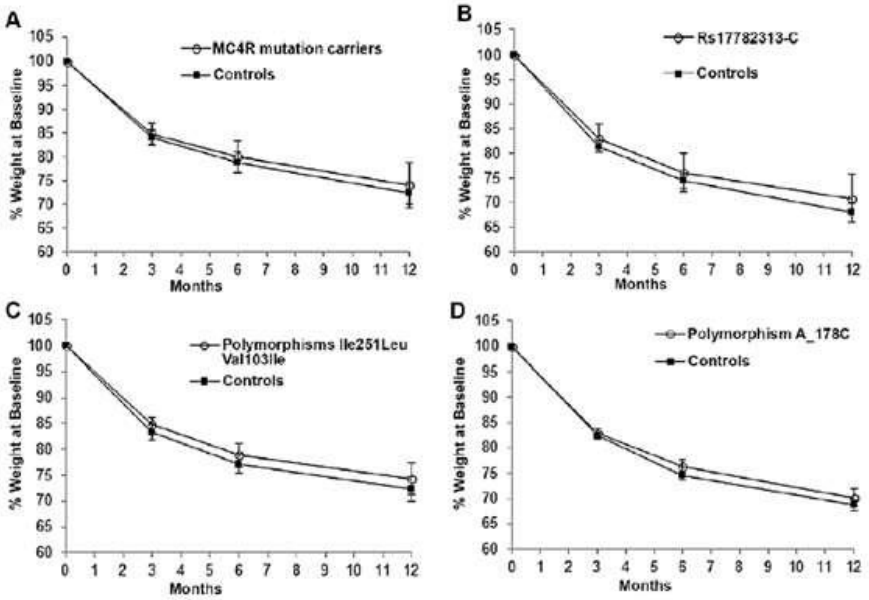
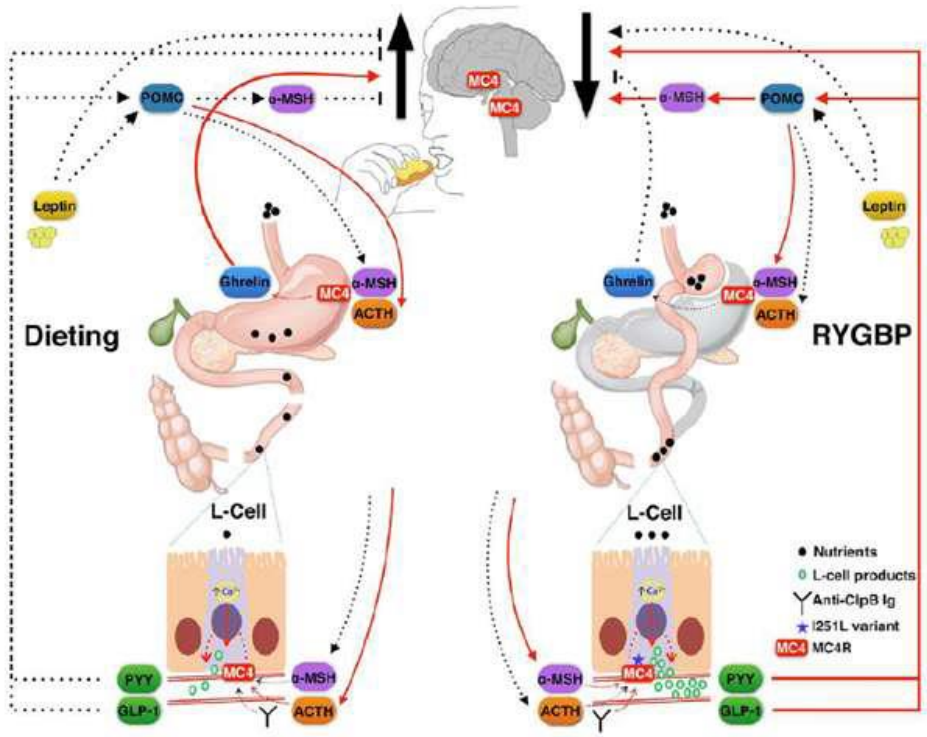


Figure 1 Weight loss following gastric bypass surgery in a man with severe super-obesity associated with melanocortin-4 receptor mutation. %EWL, percentage excess weight loss.

Melanocortin-4 receptor mutations and polymorphisms do not affect weight loss after bariatric surgery
(Vallete et al, 2012)
PLOS ONE 7(11):e48221

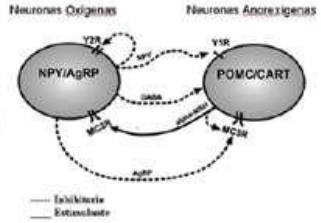



POMC
α-MSH
MC4
MC4
α-MSH
POMC
Leptin
Leptin
Ghrelin
MC4
α-MSH
ACTH
Ghrelin
MC4
α-MSH
ACTH
Dieting
RYGBP
L-Cell
L-Cell
Nutrients
L-cell products
Anti-ClpB Ig
I251L variant
MC4 MC4R
PYY
GLP-1
MC4
α-MSH
ACTH
α-MSH
ACTH
MC4
PYY
GLP-1

GAD2 gene sequence variations are associated with eating behaviors and weight gain in women from the Quebec family study.

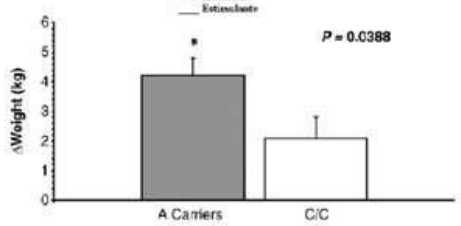
(Choquette et al, 2009)

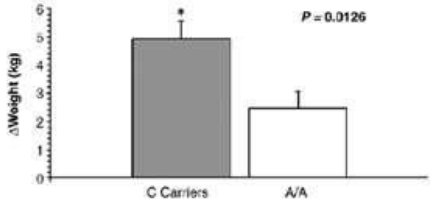
Physiology & behavior 98:505-510

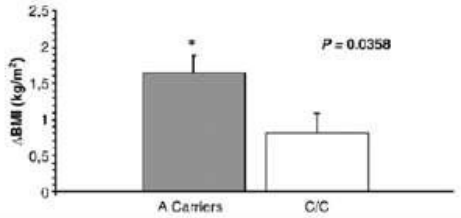


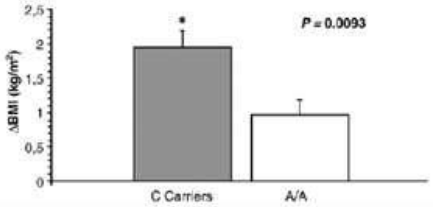
rs992990	C/C	A/C	A/A	p
Huger sensitivity	3,6	4,2	5,2	0,022
Emotional sensitivity	1,3	1,3	2,0	0,0015

rs7908975	A/A	C	p
Situational sensitivity	1,8	2,3	0,011
Emotional sensitivity	1,3	1,6	0,031









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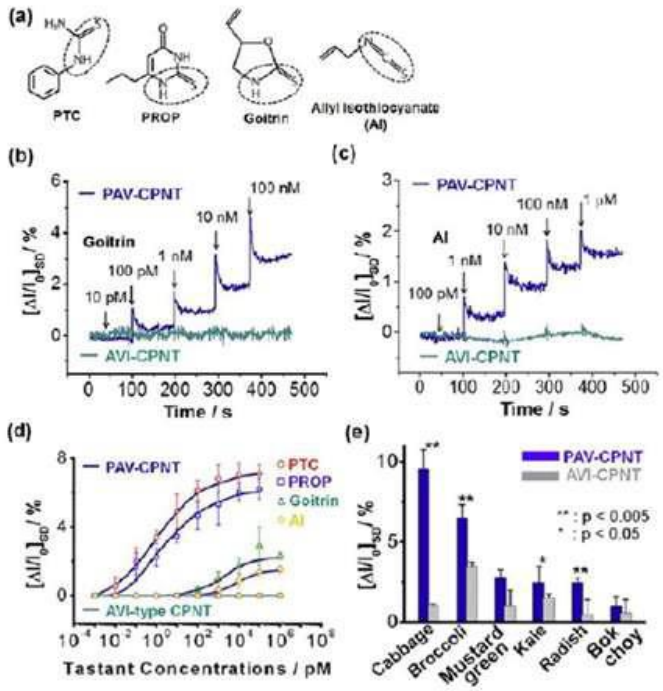
Comparison between values at 0800 and 2200 h in normal feeding (three meals)

	0800 h	2200 h	*P*
Leptin (ng/ml)	6.43 ± 0.74	8.77 ± 0.87	<0.001
Female subjects	8.83 ± 1.00	11.40 ± 1.00	<0.001
Male subjects	3.47 ± 0.66	5.51 ± 1.16	<0.001
Taste recognition thresholds (mmol/l)			
Sucrose	23.0 ± 2.5	38.2 ± 4.0	<0.001
Glucose	95.3 ± 7.7	156.9 ± 20.0	<0.001
Saccharin	0.087 ± 0.011	0.15 ± 0.03	<0.05
NaCl	24.8 ± 2.7	24.8 ± 4.0	NS
Citric acid	0.47 ± 0.06	0.57 ± 0.09	NS
QHCl	0.012 ± 0.001	0.013 ± 0.002	NS
MSG	4.2 ± 0.6	5.3 ± 0.8	NS

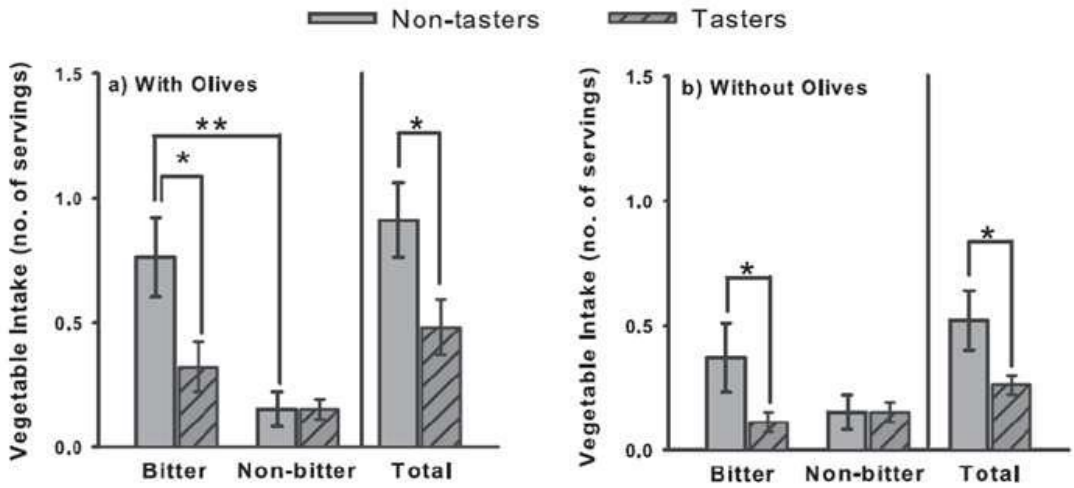
Genetic variation in gene TAS2R38



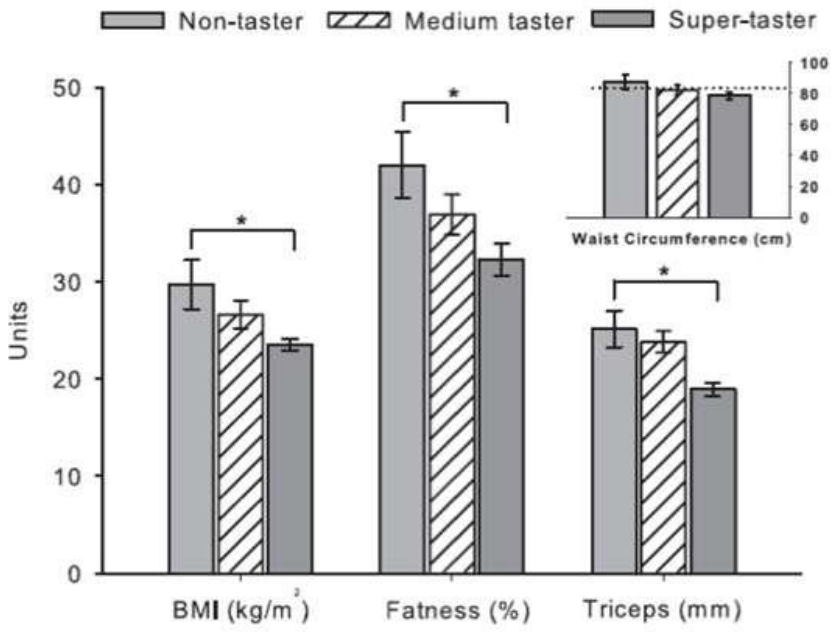
A paper screening test to assess genetic taste sensitivity to 6-n-propylthiouracil.
Physiology & behavior 2003, 78:625-633

0,032 mM Homozygotes
0,32 mM Heterozygotes
3,2 mM Homozygotes

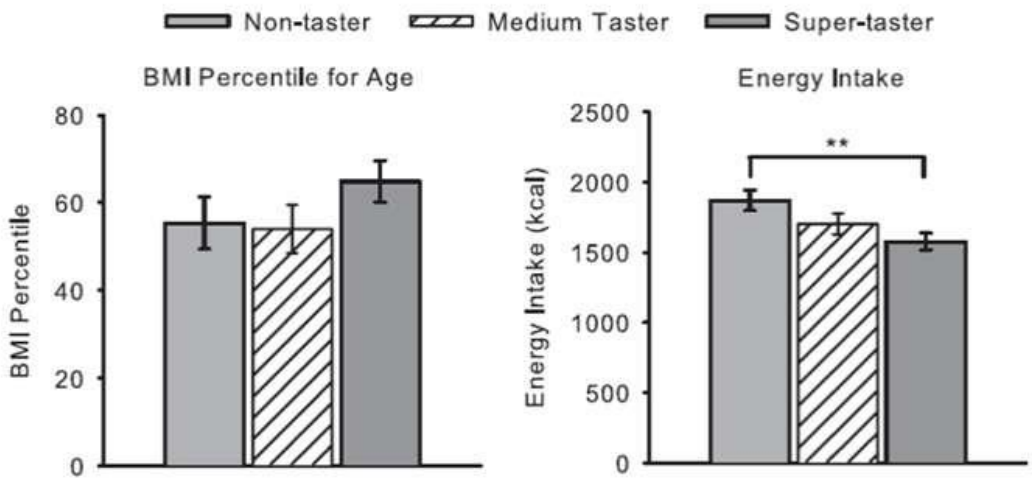
Implications for food choice



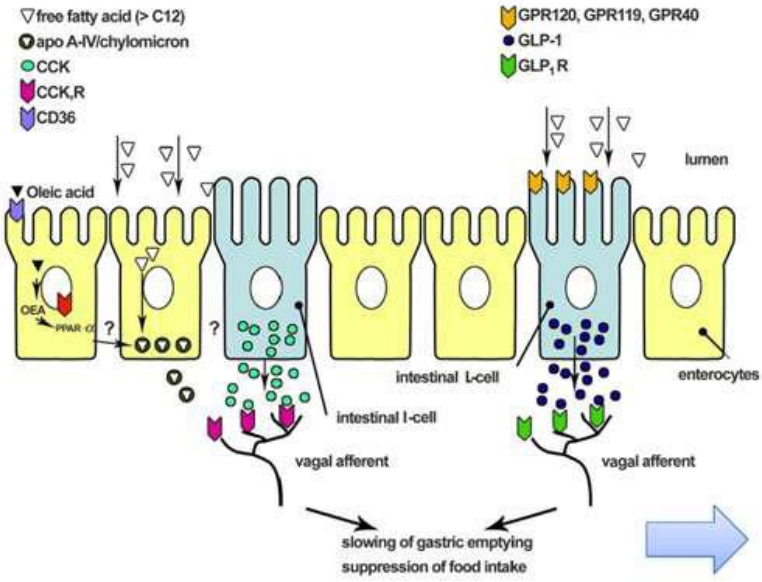
Implications for young women



Implications for teenagers



Oral and gastrointestinal sensing of dietary fat and appetite regulation in humans: modification by diet and obesity
(Little & Feinle-Bisset, 2010)
Front Neurosci 4, 178-178.



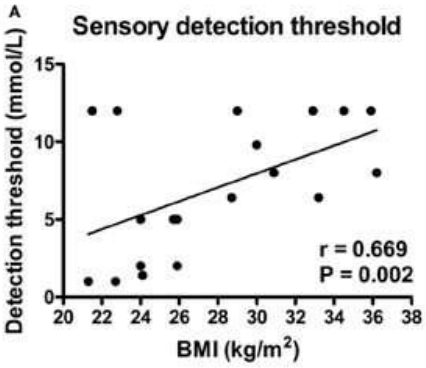
Ghrelin secretion regulation, GLP-1, and gastric distension

Oral sensitivity to oleic acid is associated with fat intake and body mass index

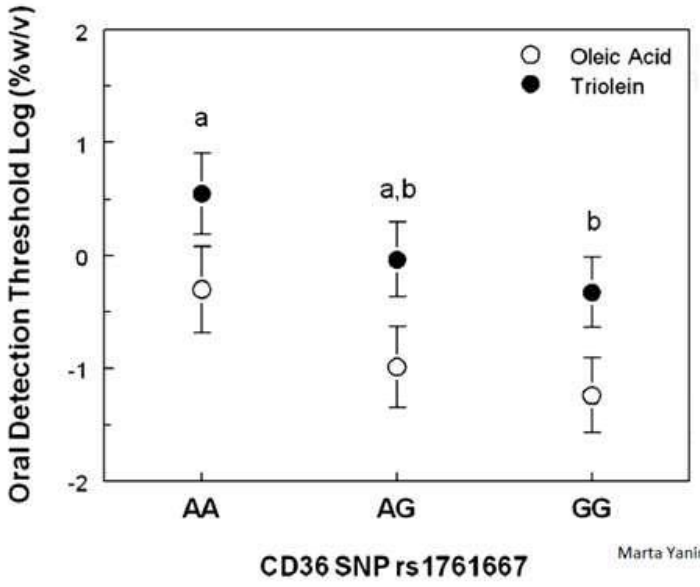
(Stewart et al, 2011)
Clinical Nutrition 30 (2011) 838-844

Nutrient/Food	Hyposensitive (n=38)	Hypersensitive (n=13)
Energy (kJ)	9355 ± 540	7188 ± 791
Fats (g)	76 ± 4	62 ± 5
Whole dairy products (g/day)	542 ± 64	396 ± 63
Meat (g/day)	229 ± 36	96 ± 30
Eggs (g/day)	53 ± 15	16 ± 6

	Hyposensitive		Hypersensitive	
	Women	Men	Women	Men
BMI	21,8 ± 0,6	23,9 ± 1,3	20,4 ± 0,6	22,3 ± 0,7



Oleic acid (open symbol) and triolein (closed symbol) detection thresholds in individuals who are homozygous for the allele associated with low (AA, n = 6) or high (GG, n = 8) CD36 expression levels and in heterozygous subjects (AG, n = 7).

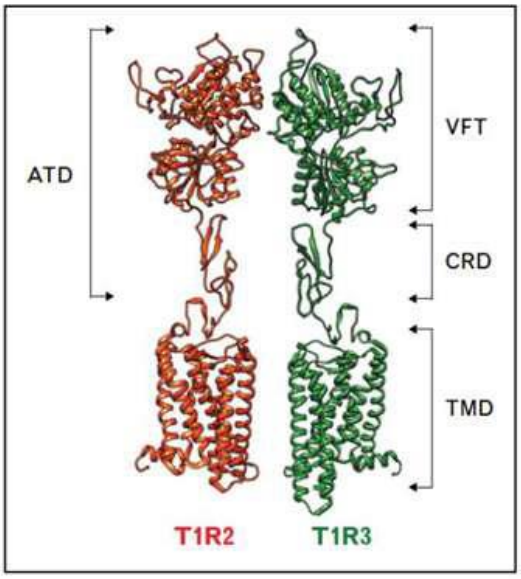


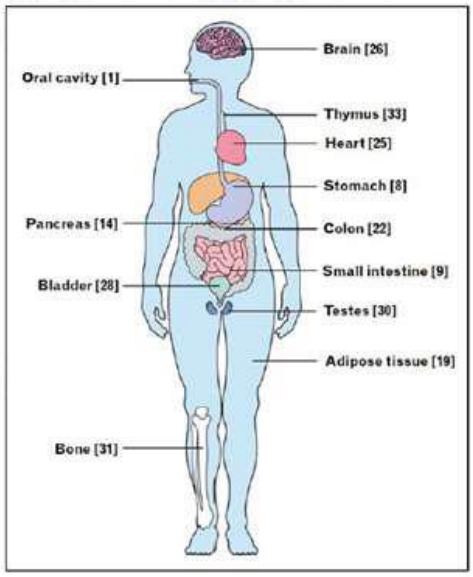
Marta Yanina Pepino et al. J. Lipid Res. 2011;53:561-566

Functional roles of the sweet taste receptor in oral and extraoral tissues

(Laffitte, 2014)

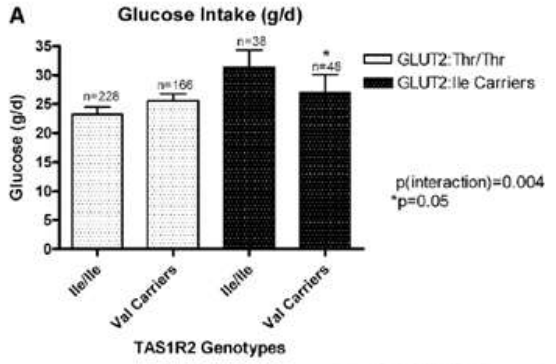
Curr Opin Clin Nutr Metab Care. 17:379-85

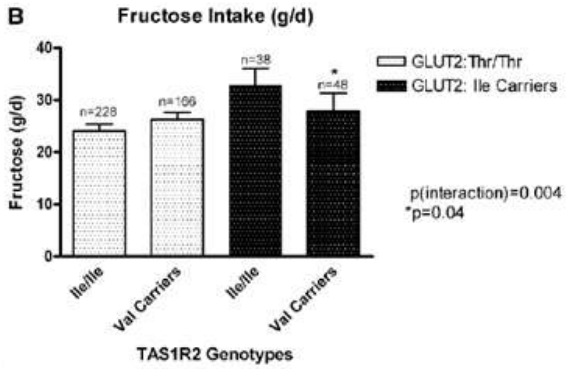




Genetic variation in TAS1R2 (Ile191Val) is associated with consumption of sugars in overweight and obese individuals in 2 distinct populations

(Eny et al, 2010)
Am J Clin Nutr. 92:1501-10



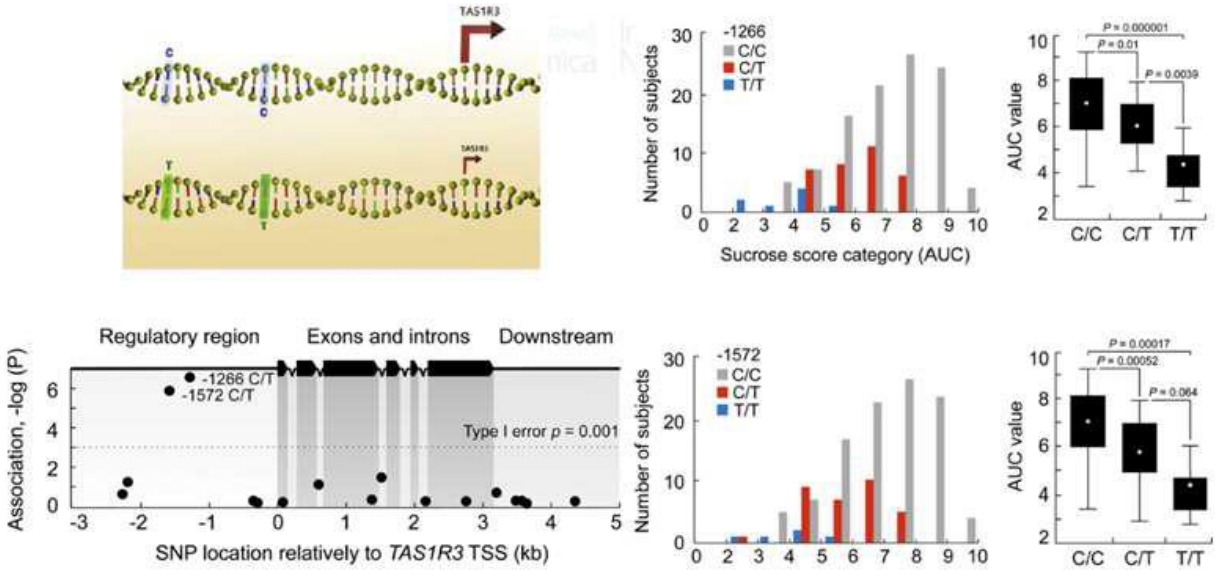


TAS1R2: rs35874116
GLUT2: rs5400

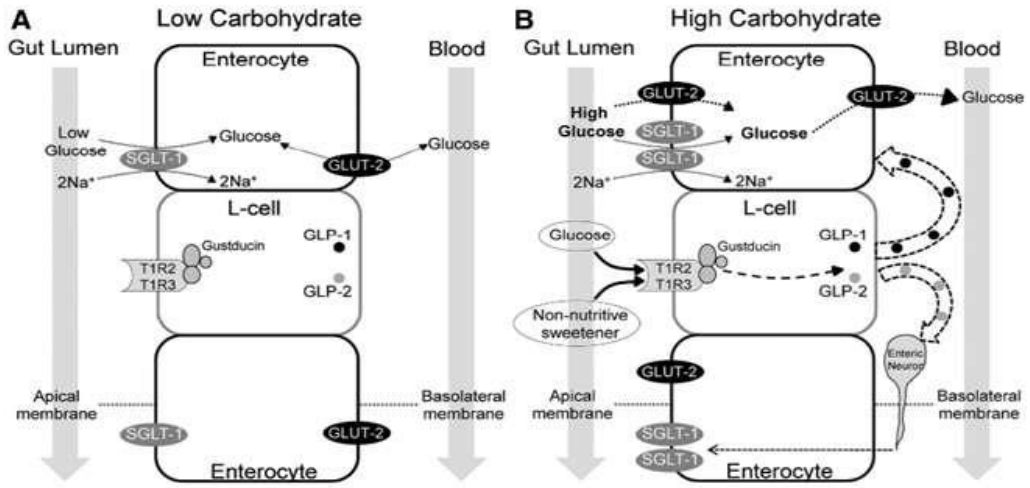
Comparison of 1-mo daily average servings from sugar-containing food groups for Ile191Val genotypes in overweight subjects in population 1[1]

	Ile/Ile (n = 103)	Val carriers (n = 102)	P
Dairy products	1.39 ± 0.13	1.27 ± 0.14	0.15[2]
Fruit juice	0.57 ± 0.12	0.42 ± 0.12	0.30[3]
Sweetened beverages	0.47 ± 0.07	0.44 ± 0.07	0.64[2]
Sweets	1.14 ± 0.11	0.98 ± 0.11	0.23[3]

Allelic polymorphism within the TAS1R3 promoter is associated with human taste sensitivity to sucrose
(Fushan et al, 2009)
Curr Biol 19:1288-1293



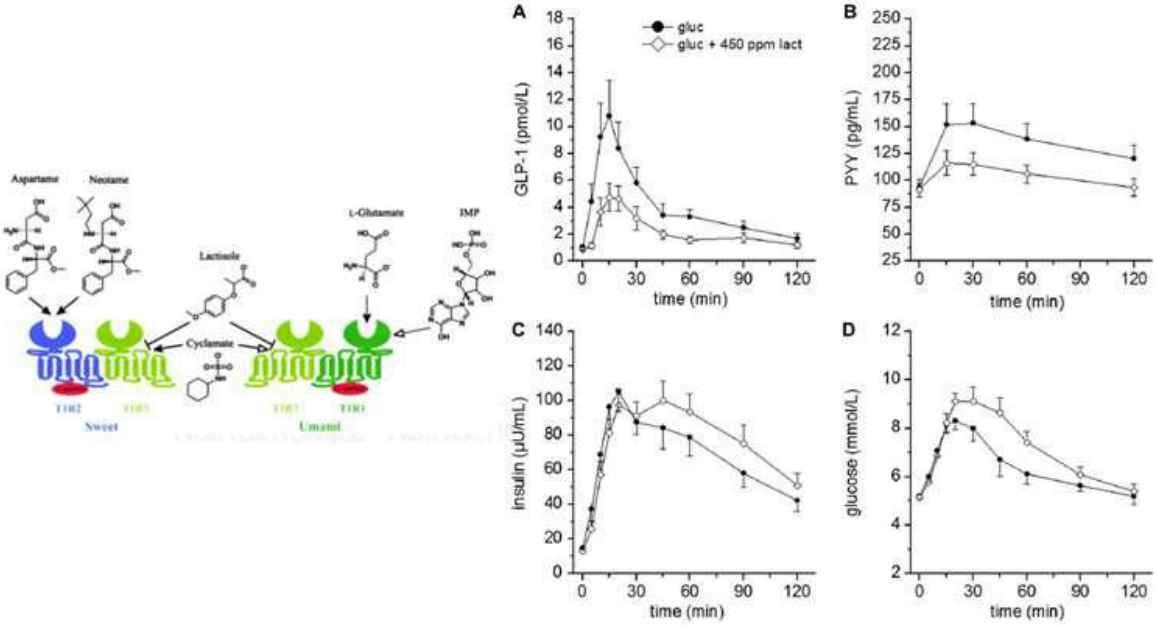
Role of Sweet Taste in Satiation and Satiety



The functional involvement of gut-expressed sweet taste receptors in glucose-stimulated secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)

(Steinert et al, 2011)

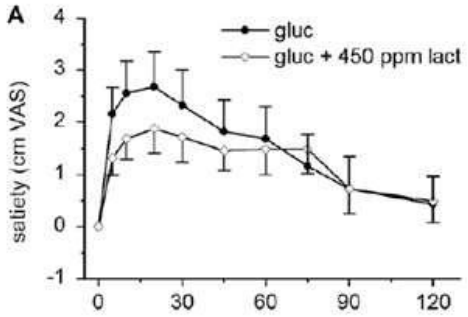
Clin Nutr 30:524-532

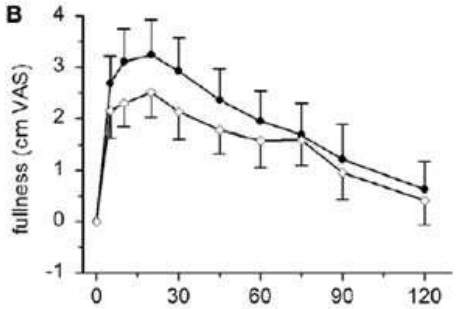


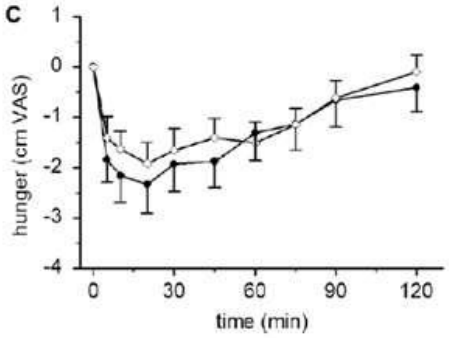
The functional involvement of gut-expressed sweet taste receptors in glucose-stimulated secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY)

(Steinert et al, 2011)

Clin Nutr 30:524-532



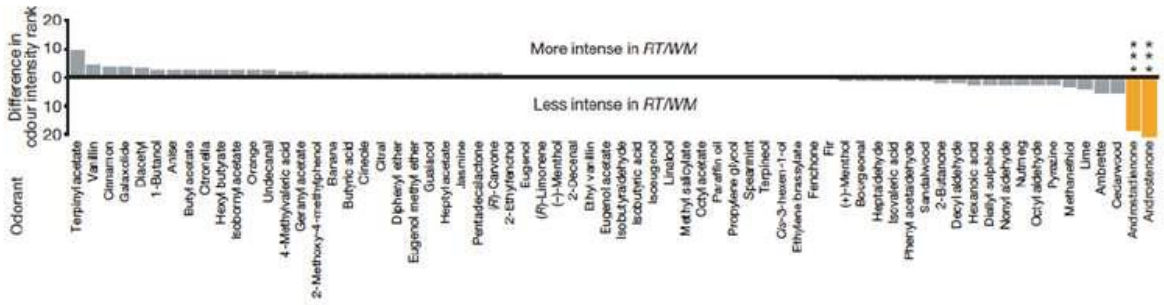




Association between olfactory receptor genes, eating behavior traits and adiposity: Results from the Quebec Family Study.
(Choquette et al, 2012)
Physiology & Behavior 105:772-776

OR7D4
rs2878329

	A	(G/C)
Hunger	3,3	4,2
BMI	26,9	28,2
Circumference Waist (cm)	86,4	90,4
Fat percentage	26,9	28,9



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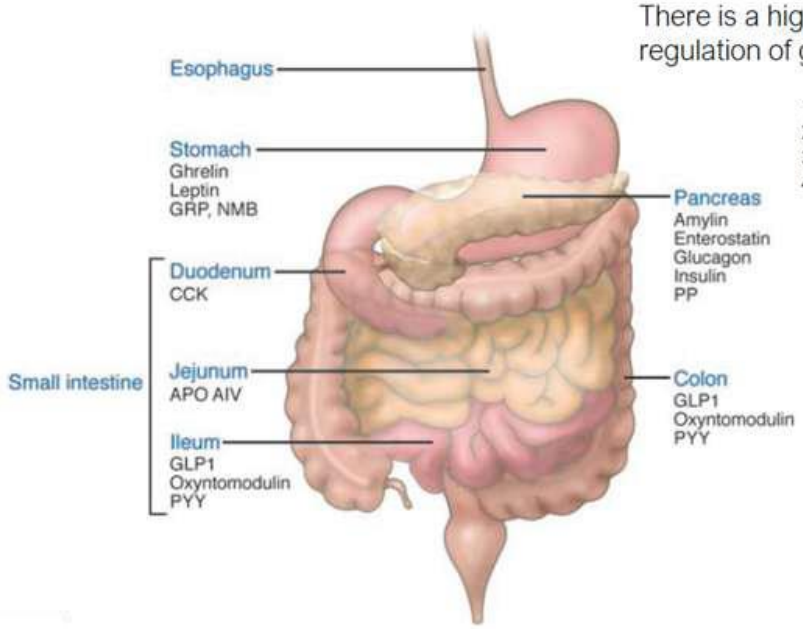
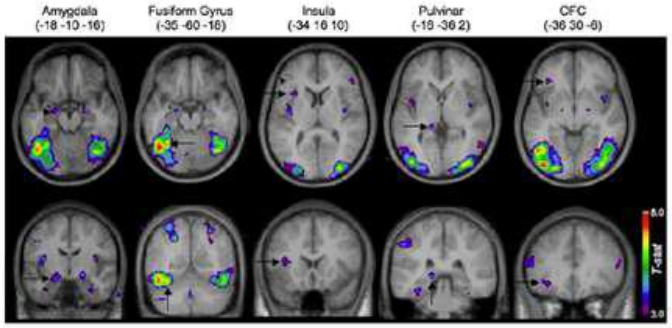
Physiology of gastrointestinal satiety hormones

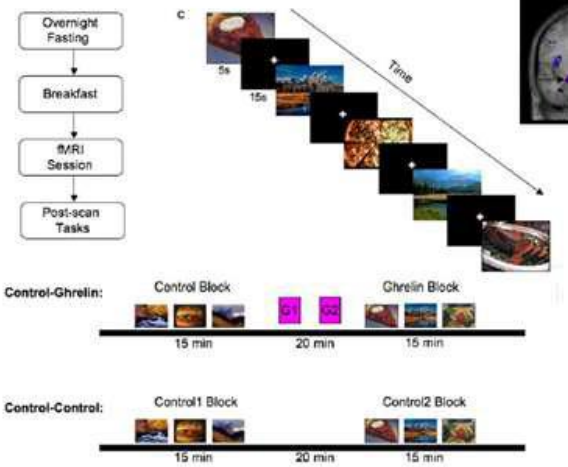


There is a high interest in the functioning and regulation of gastrointestinal or gut hormones

1. Short-term actions
2. High effect on satiety signals
3. They do not induce resistance
4. Largest endocrine organ (more than 20 hormones)

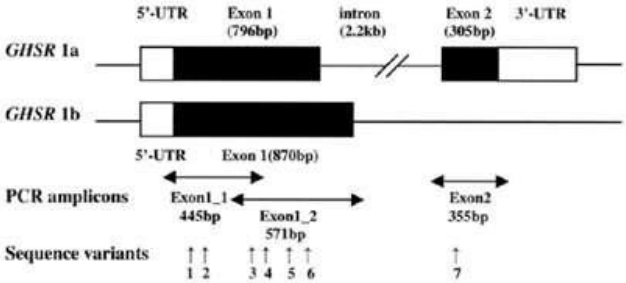
Ghrelin modulates brain activity in areas that control appetitive behavior
(Malik et al, 2008)
Cell Metabolism 7:400-409





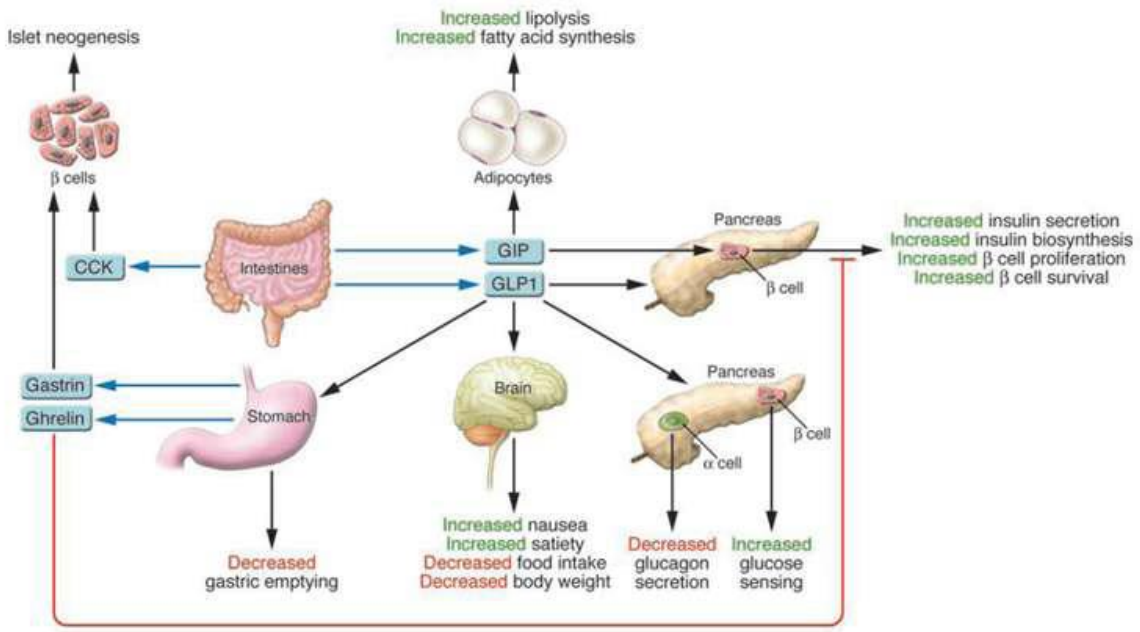
Ghrelin Receptor Gene: Identification of Several Sequence Variants in Extremely Obese Children and Adolescents, Healthy Normal-Weight and Underweight Students, and Children with Short Normal Stature

(Wang et al, 2004)
J Clin Endocr Metabol 89:157-162

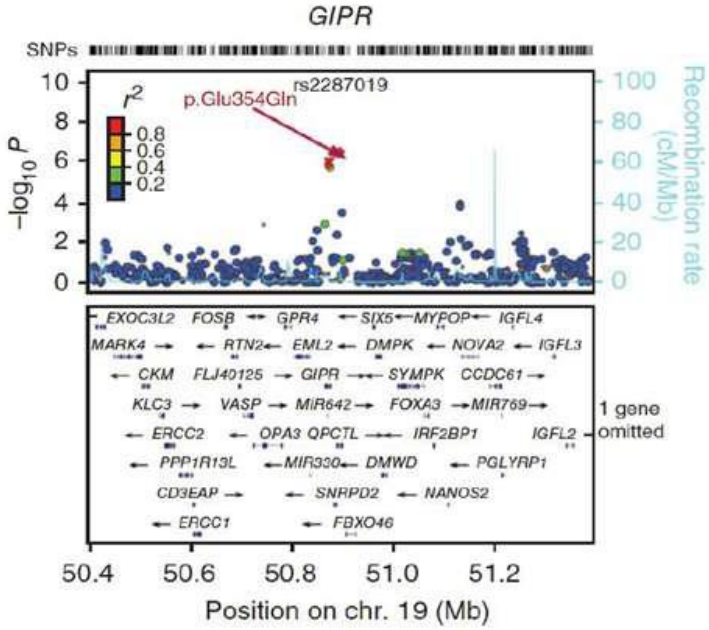


	Genotype frequencies		
	TT	TC	CC
Extremely obese children and adolescents (n = 746)	397 (53.2)	296 (39.7)	53 (7.1)
Underweight students (n = 232)	116 (50.0)	95 (41.0)	21 (9.0)
Normal-weight students (n = 96)	53 (55.2)	33 (34.4)	10 (10.4)
Children with short normal stature (n = 43)	28 (65.1)	12 (27.9)	3 (7.0)

Physiology of Incretins



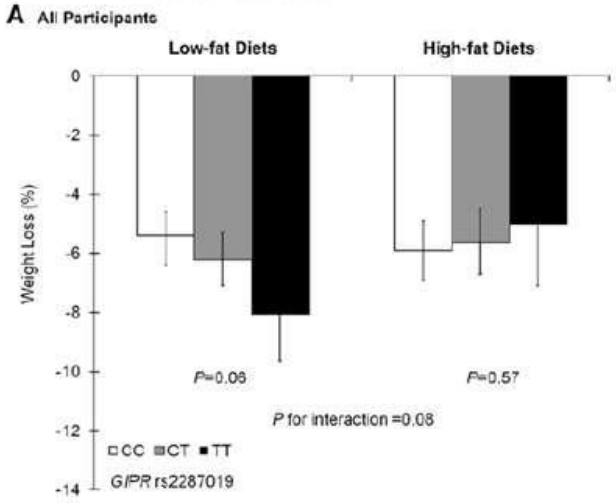
Association analyses of 249,796 individuals reveals 18 new loci associated with body mass index
(Speliotes et al, 2010)
Nat Genet 42:937-948



Weight-loss diets modify glucose-dependent insulinotropic polypeptide receptor rs2287019 genotype effects on changes in body weight, fasting glucose, and insulin resistance: the Preventing Overweight Using Novel Dietary Strategies trial.

(Qi et al, 2012)

Am J Clin Nutr 95:506-513



Macronutrient distribution

	Low-fat	High-fat
Fats	20%	40%
Proteins	15-25%	15-25%
Carbohydrates	65-55%	45-35%

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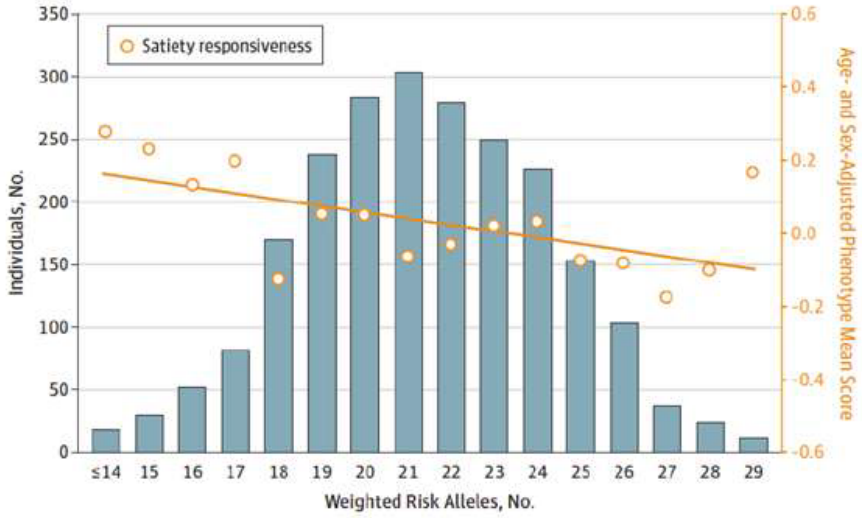
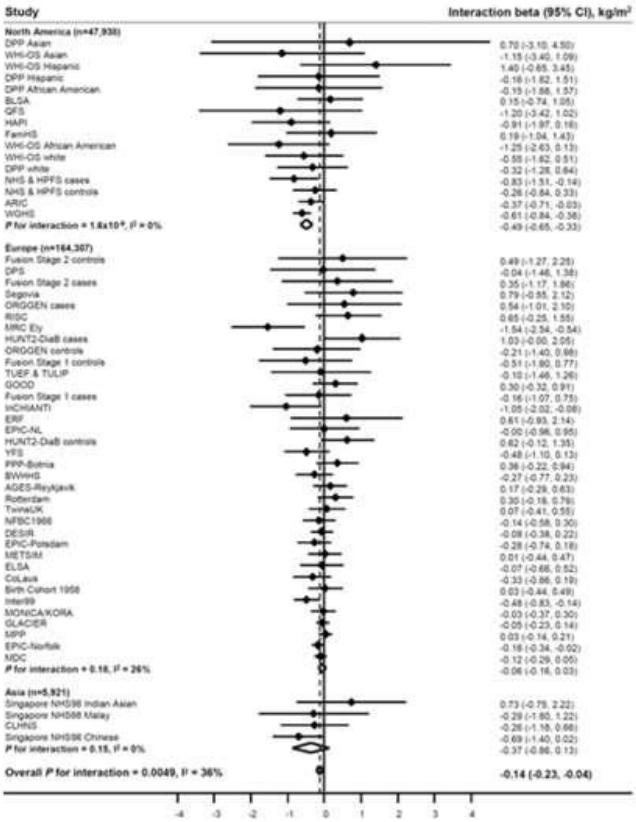
Satiety mechanism in genetic risk of obesity
(Llewellyn et al, 2014)
JAMA Pediatr 168(4):338-344

rs9939609 (FTO)
rs2867125 (TMEM18)
rs571312 (MC4R)
rs10938397 (GNPDA2)
rs10767664 (BDNF)
rs2815752 (NEGR)
rs7359397 (SH2B1)
rs3817334 (MTCH2)
rs29941 (KCTD15)
rs543874 (SEC16B)
rs987237 (TFAP2B)
rs7138803 (FAIM2)
rs10150332 (NRXN3)
rs713586 (POMC)
rs12444979 (GPRC5B)
rs2241423 (MAP2K5)
rs1514175 (TNNI3K)
rs109968576 (LRRN6)
rs887912 (FANCL)
rs13078807 (CADM2)
rs1555543 (PTBP2)
rs206936 (NUDT3)
rs9568856 (OLFM4)
rs9299 (HOXB5)
rs2112347 (FLJ35779)
rs4836133 (ZNF608)
rs4929949 (RPL27A)
rs3810291 (TMEM160)
rs2890652 (LRP1B)
rs9816226 (ETVB5)
rs13107325 (SLC39A8)
rs4771122 (MTIF3)
rs11847697 (PRKD1)
rs2287019 (QPCTL)



Forest plot of the effect of the interaction between the FTO rs9939609 SNP and physical activity on BMI in a random effects meta-analysis of 218,166 adults.



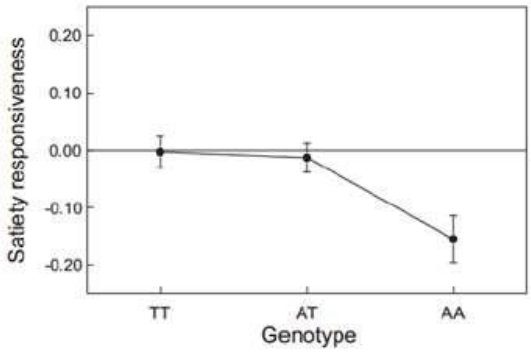
Kilpeläinen TO, Qi L, Brage S, Sharp SJ, Sonestedt E, et al. (2011) Physical Activity Attenuates the Influence of FTO Variants on Obesity Risk: A Meta-Analysis of 218,166 Adults and 19,268 Children. PLoS Med 8(11): e1001116. doi:10.1371/journal.pmed.1001116
http://journals.plos.org/plosmedicine/article?id=info:doi/10.1371/journal.pmed.1001116

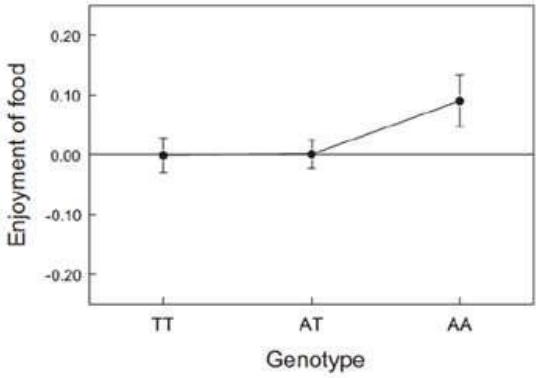
PLOS | MEDICINE

Obesity associated genetic variation in FTO is associated with diminished satiety
(Wardle et al, 2008)
J Clin Endocrinol Metab 93(9):3640-3643.

FTO rs9939609

	TT (n=1209)	AT (n=1641)	AA (n=487)	Significance
BMI	17,18	17,78	17,91	p=0,059
BMI (SD score)	-0,123	0,073	0,242	p < 0,001

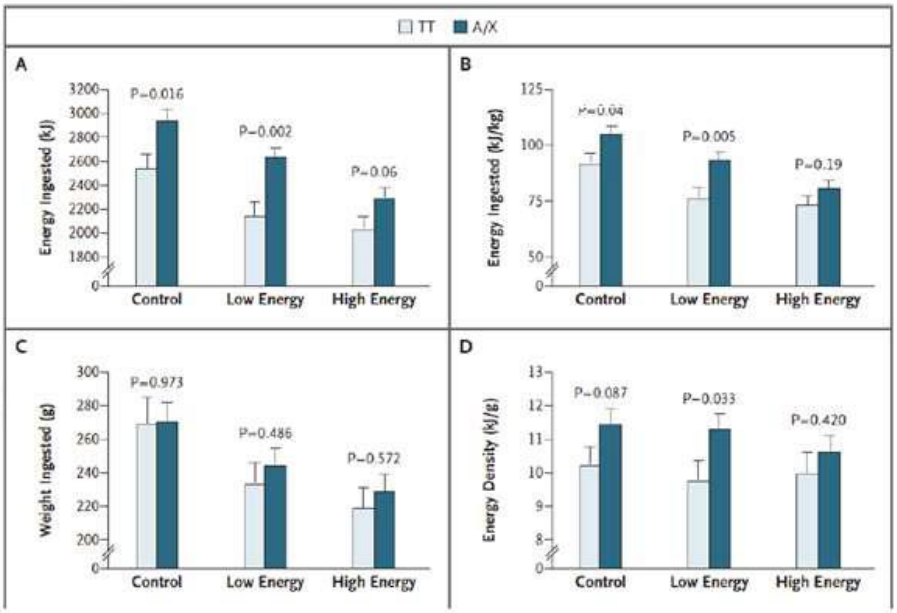




An obesity-associated FTO gene variant and increased energy intake in children
(Cecil, 2008)
N Engl J Med 359:2558-2566

FTO rs9939609

	BMI
TT (n=1016)	17,09
AT (n=1322)	17,17
AA (n=388)	17,58
Signif.	p=0,003



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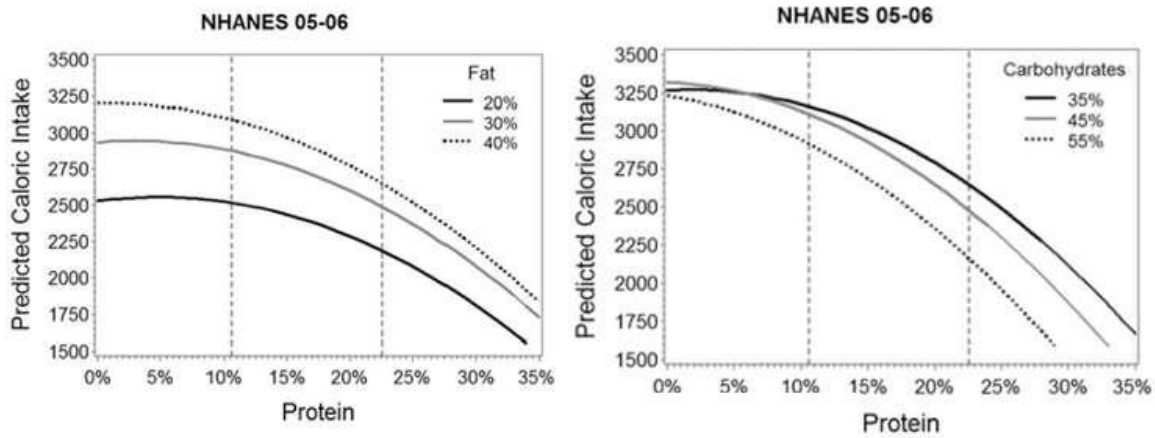
Improving glucose tolerance by reducing weight gain in a polygenic obese mouse model: use of a high protein diet
(Blair et al, 2015)
Horm Metab Res, 47:184-193

Hypotehsis: An individual will continue eating until he takes in his/her protein needs. Consequently, low-protein diets can lead to a high carbohydrate and fat intake.

Trends in carbohydrate, fat and protein intakes and association with energy intake in normal-weight, over-weight and obese individuals: 1971-2006.

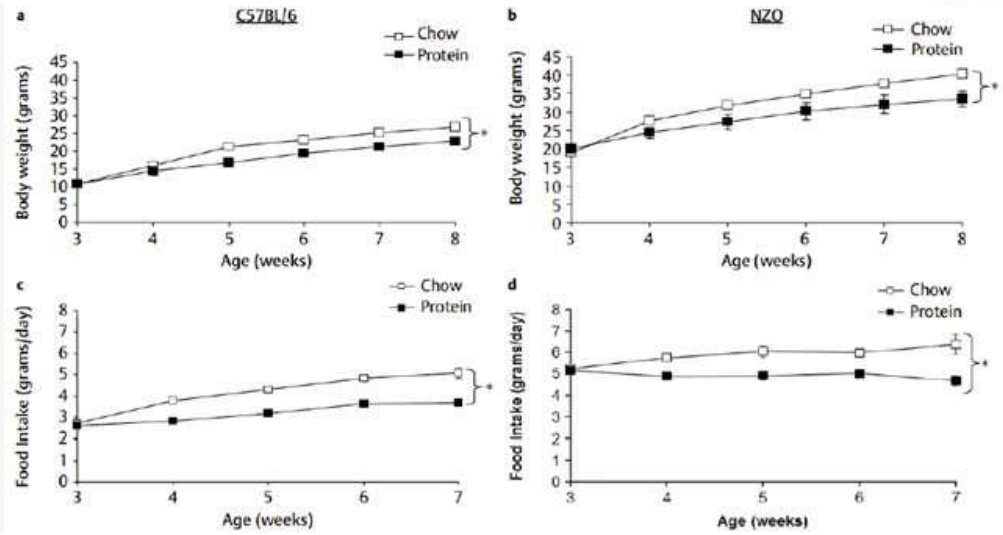
(Austin et al, 2011)

Am J Clin Nutr 93:836-843.



Improving glucose tolerance by reducing weight gain in a polygenic obese mouse model: use of a high protein diet
(Blair et al, 2015)
Horm Metab Res, 47:184-193

New Zealand Obese (NZO)
Pctp, Tbc1d1, Zfp69, Ifi202b,
Lepr, Abcg1, Nmur2,



Trends in functional food against obesity: functional ingredients, technologically modified foods and complete diets a(Serrano et al, 2008)

Revista de Española de Nutrición Comunitaria 14 (3): 193-200. July 2008

Reduction in food energy density	-Reducing fat content -Replacing simple sugars with sweeteners with no caloric value -Increasing fiber content -Increasing water content
B. Technological-sensory modification	-Texture modification -Reducing density (increase in air content)
C. Modification of the content of macronutrients in order to cause satiety	-Increasing protein content
D. Modification of the food glycemic index	-Adding fibers or ingredients that slow the absorption of carbohydrates in the small intestine
E. Inclusion of functional ingredients	-Suppressing appetite (blocking orexigenic signals or increasing anorexigenic signals) -Restricting nutrient bioavailability, using digestive enzymes inhibitors. -Stimulating energy expenditure (thermogenesis) -Modifications in the colonic microbiota composition
F. Complete diets	-Preparation of foods/dishes nutritionally balanced and complete that can substitute some meal times and that combine several functional ingredients which provide a better energy and nutrient intake control as well as metabolic expenditure.

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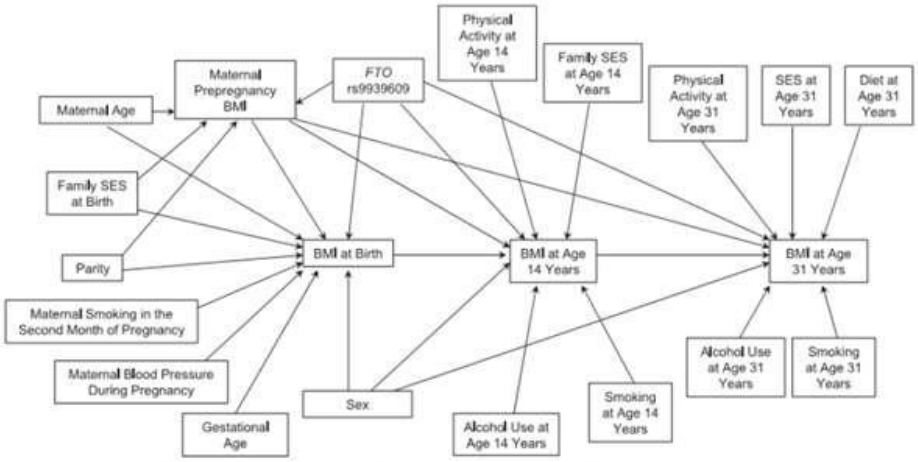
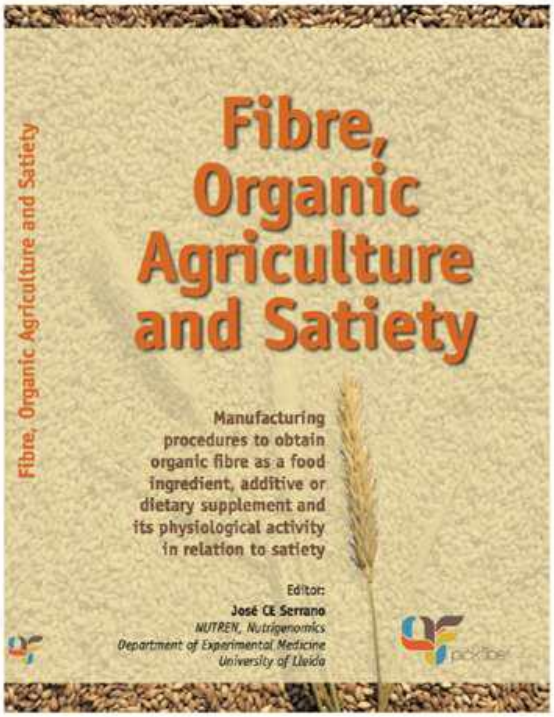
Conclusions

Dynamic Genotype Obesity



Paradoxically, the appetite of obese people who follow a low-calorie diet usually decreases.



https://www.google.es/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0ahUKEwjn1KTOy_LOAhXDVhoKHbhkDrYQFggoMAI&url=http%3A%2F%2Fwww.nutren.udl.cat%2Fftp%2Fpdf%2FPICKFIBERHandbook_printed.pdf&usg=AFQjCNHD-MMyNGR7JGCtxlKbdn4VnUQZww

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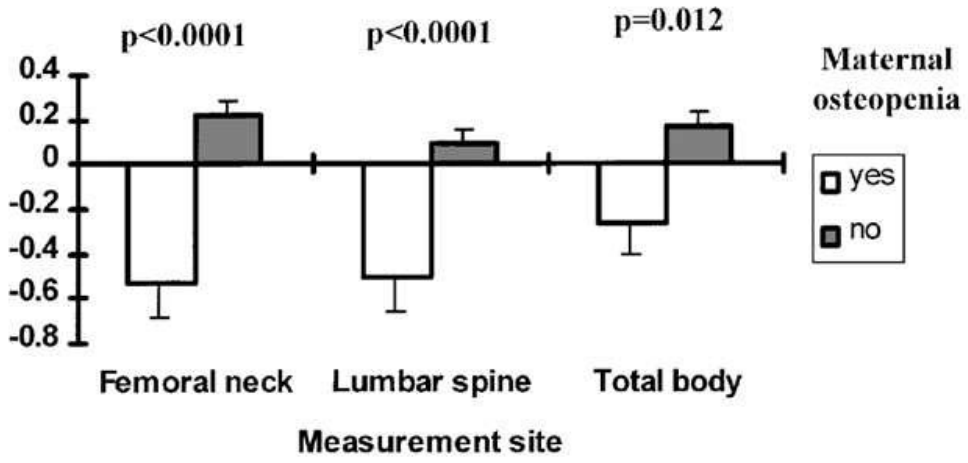
Associations between maternal peak bone mass and bone mass in prepuberal male and female children

(Jones & Nguyen, 2000)

J Bone Miner Res 15:1998-2004



Genes associated to changes in bone mass

	Gene	Protein
Calciotropic hormones and receptors	*VDR*	vitamin D receptor (VDR)
	ER-α	Estrogen receptor alpha
	ER-β	Estrogen receptor beta
	CT	Calcitonin
	CTR	Calcitonin receptor
	PTH	Parathormone / parathyroid hormone
	PTHR1	Parathyroid hormone 1
	CYP19	Aromatase
	GCCR	Glucocorticoid receptor
	CaSR	Calcium-sensing receptor
	AR	Androgen receptor
Cytokines and growth factors	*TGF-β1*	Transforming growth factor beta 1
	IL-6	Interleukin 6
	IGF-1	Insulin-like growth factor 1
	IL-1ra	Interleukin-1 receptor antagonist
	OPG	Osteoprotegerin
	TNF-α	Tumor necrosis factor-α
	TNFR2	Tumor necrosis factor receptor 2
Proteínas de la matriz ósea	*COLIA1*	alpha-1 type I collagen
	COLIA2	alpha-2 collagen type I
	BGP	Osteocalcin
	MGP	Matrix gla protein
	AHSG	alpha-2-HS-glycoprotein

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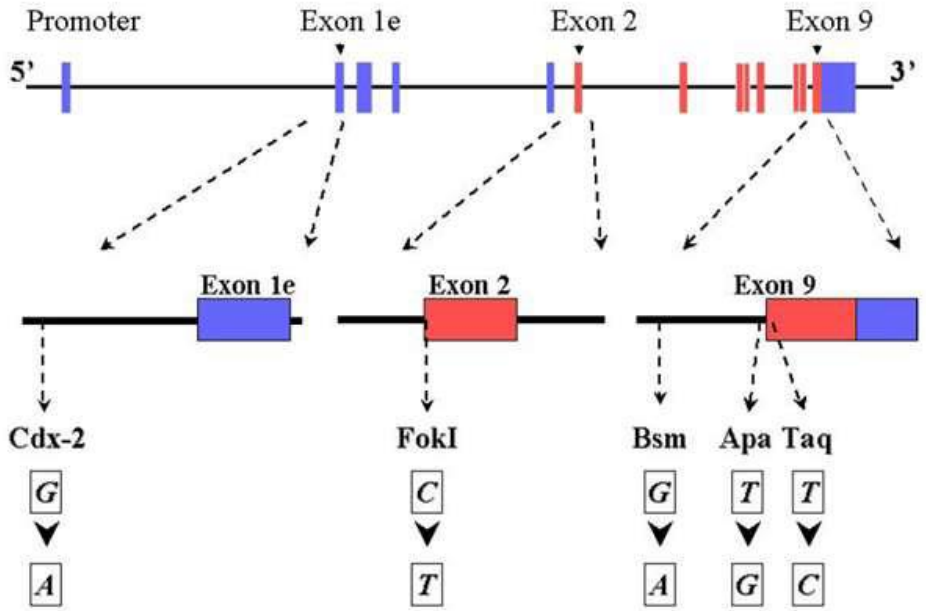
Vitamin D receptor *(VDR)*



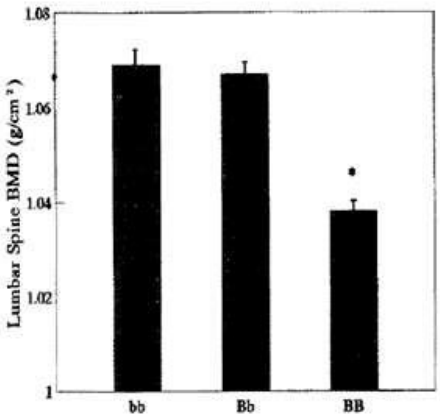
The association between vitamin D receptor gene polymporphism and bone mineral density at the spine, hip and whole-body in premenopausal women.

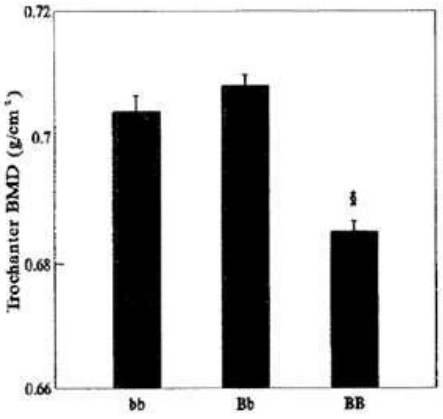
(Salomone et al, 1996)

Osteoporosis International, 6:63-68

rs1544410
bb: AA
bB: AG
BB: GG

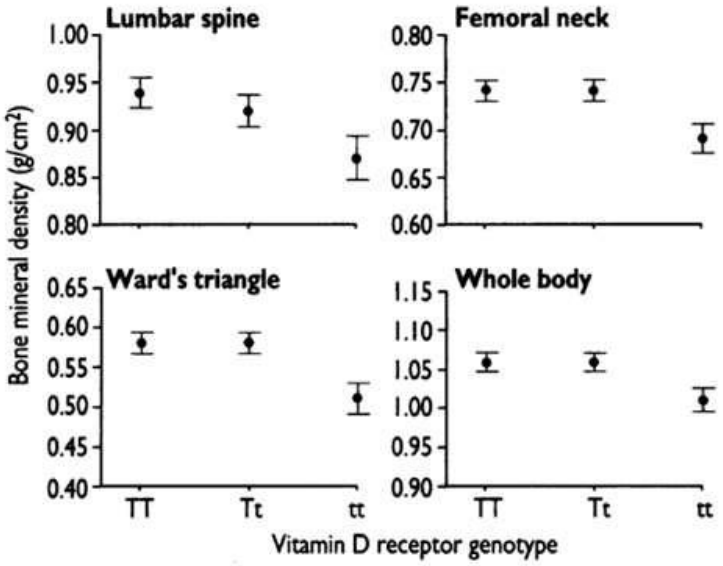
*Bms*I





Influence of vitamin D receptor genotype on bone mineral density in postmenopausal women: a twin study in Britain
(Spector et al, 1995)
BMJ 310:1357-1360

*Taq*I

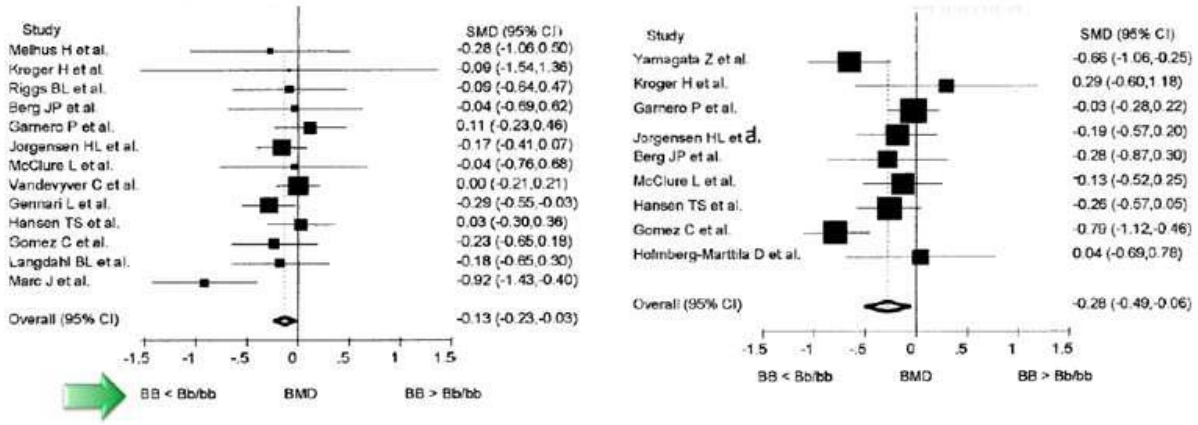


Meta-analysis of molecular association studies: vitamin D receptor gene polymorphism and BMD as a case study

(Thakkinstian et al, 2004)

J Bone Miner Res 19:419-428

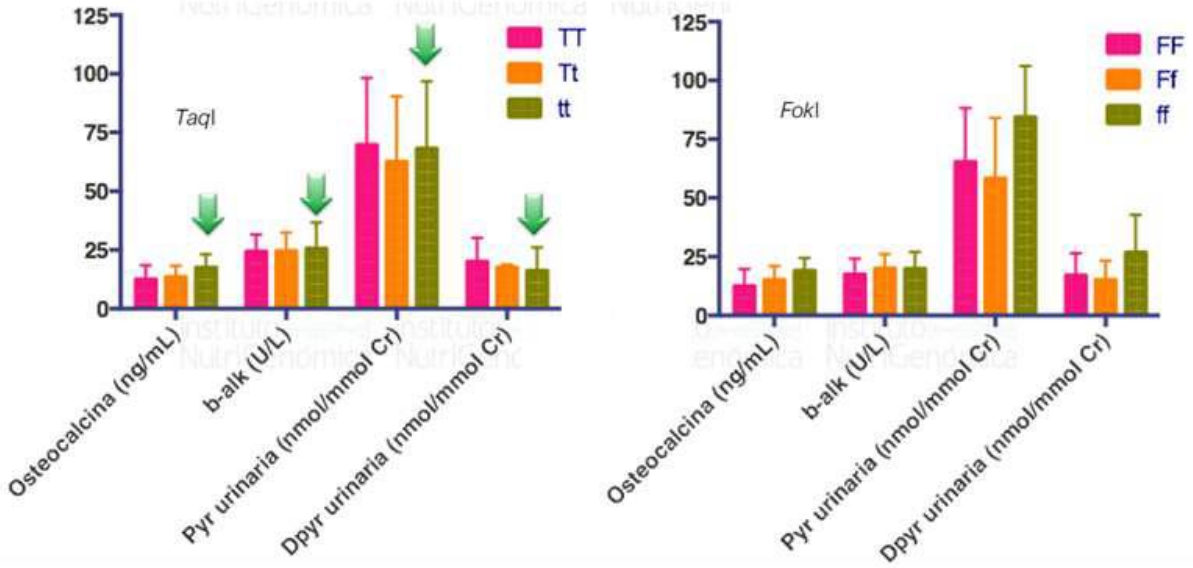
Bmsl



Cross-sectional

Longitudinal

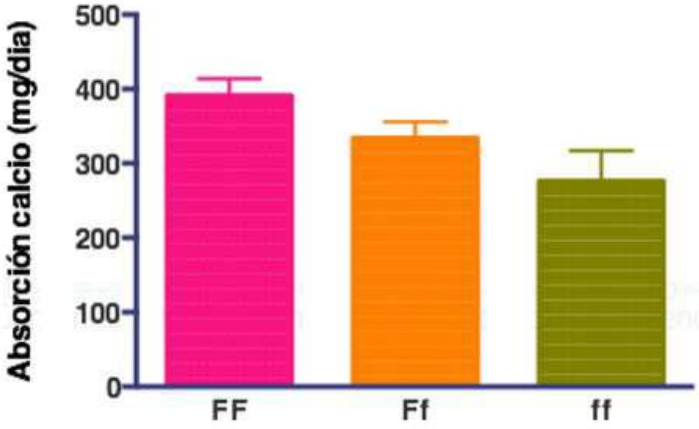
An assessment of genetic markers as predictors of bone turnover in healthy adults
(Sheehan et al, 2001)
J Endocrinol Invest 24:236-245



Vitamin D receptor gene *Fok*1 polymorphism predicts calcium absorption and bone mineral density in children

(Ames et al, 1999)

J Bone Miner Res 14;740-746

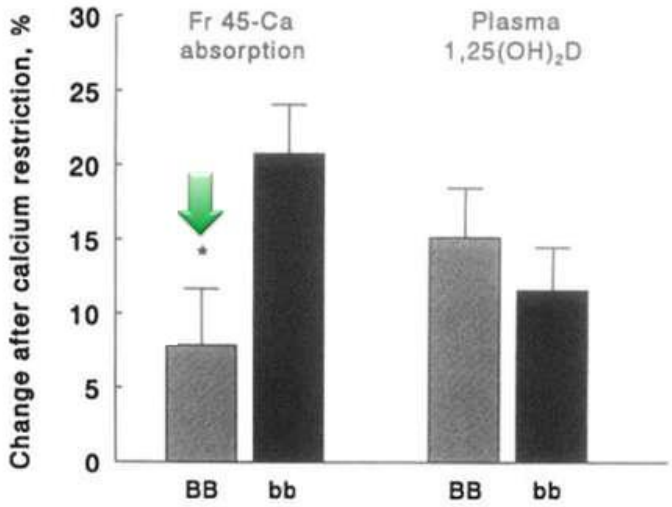


Calcium absorption on high and low calcium intakes in relation to vitamin D receptor genotype

(Dawson-Hughes et al, 1995)

J Clin Endocrinol Metab 80:3657-3661

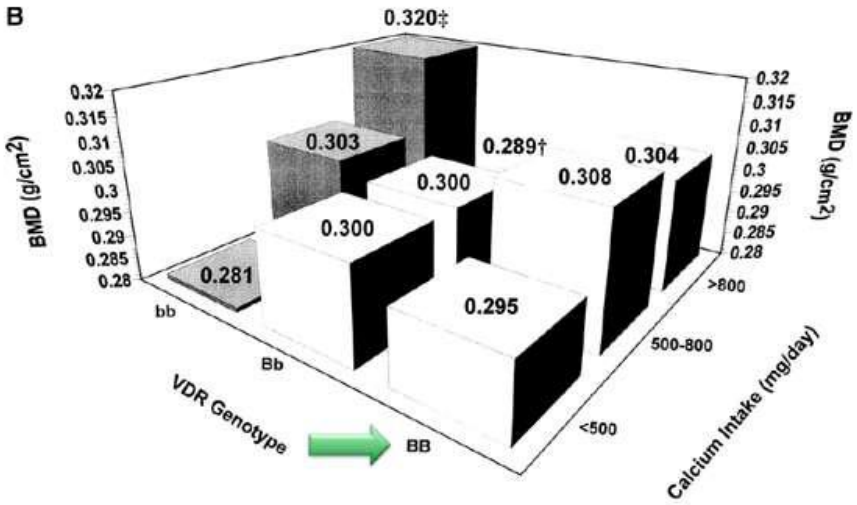
*Bms*I



The BsmI vitamin D receptor restriction fragment length polymorphism (bb) influences the effect of calcium intake on bone mineral density

(Kiel et al, 1997)

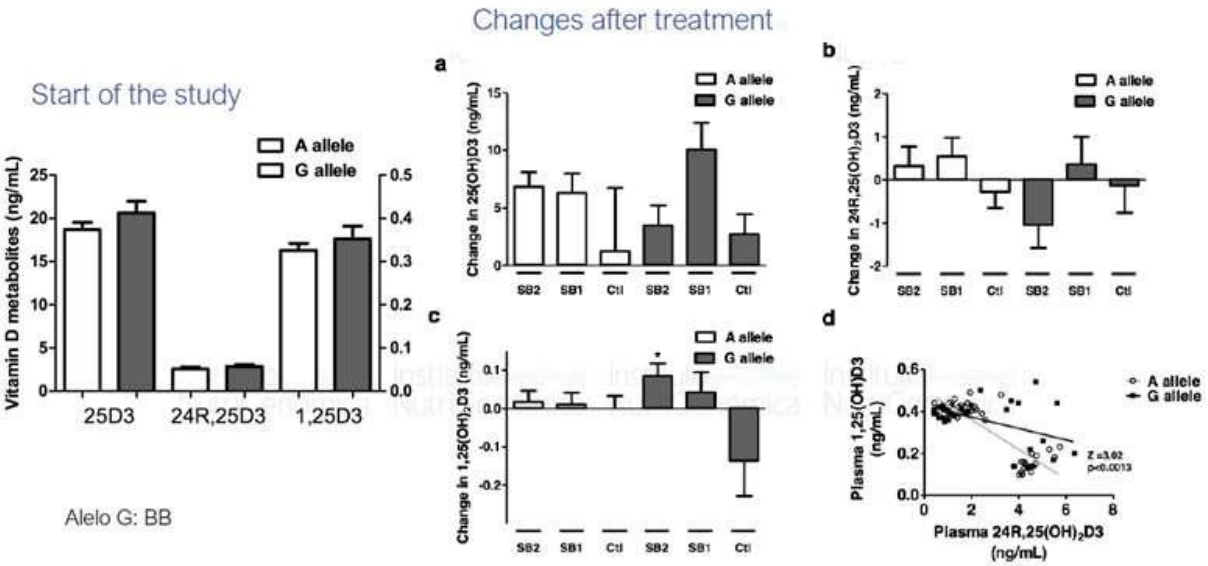
J Bone Miner Res, 12:1049-1057



Vitamin D receptor *BsmI* polymorphism modulates soy intake and 25-hydroxy vitamin D supplementation benefits in cardiovascular disease risk factors profile.

(Serrano et al, 2013)

Genes & Nutrition 8:561-569



Vitamin D receptor *Bsm*I polymorphism modulates soy intake and 25-hydroxy vitamin D supplementation benefits in cardiovascular disease risk factors profile.

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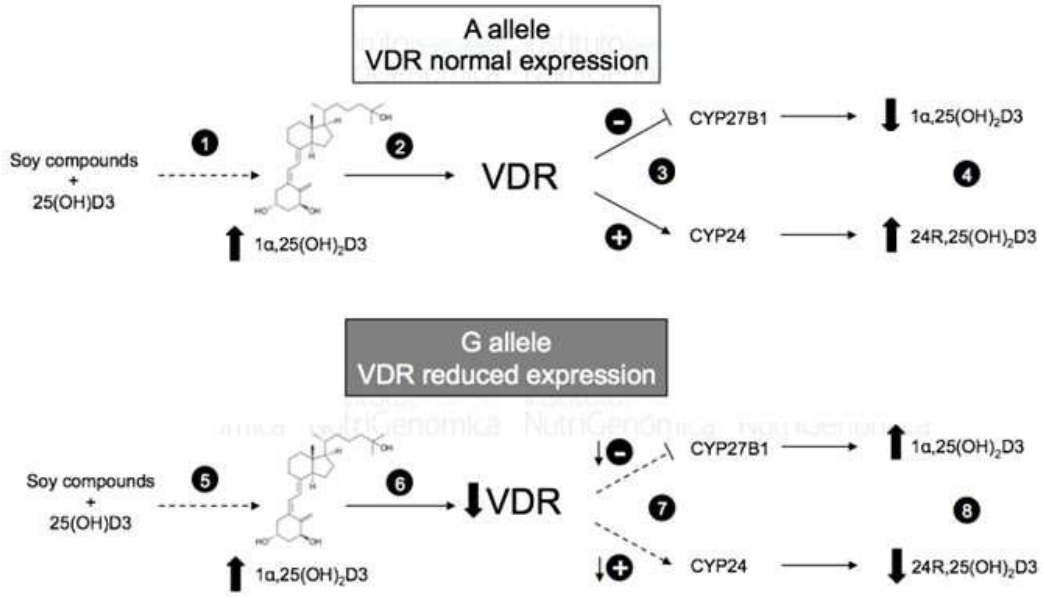
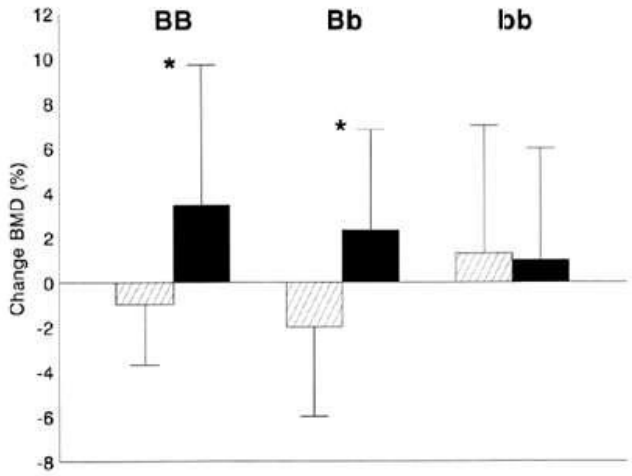
Genes & Nutrition 8:561-569



The effect of vitamin D supplementation on the bone mineral density of the femoral neck is associated with vitamin D receptor genotype

(Graafmans et al, 1997)

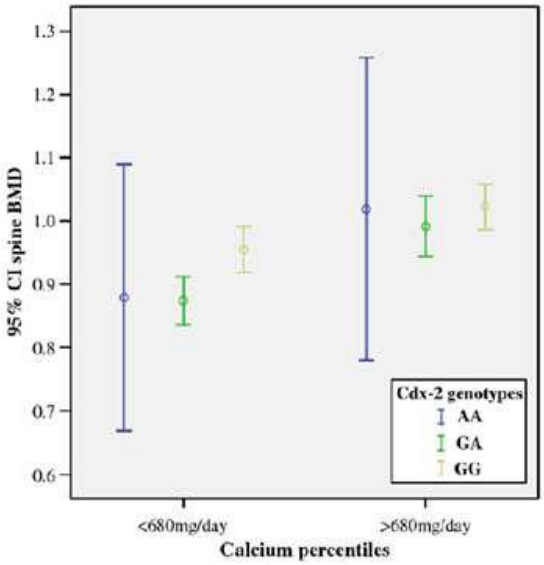
J Bone Miner Res 12:1241-1245



The role of vitamin D receptor gene polymorphisms in the bone mineral density of Greek postmenopausal women with low calcium intake

(Stathopoulou et al, 2011)

J Nutr Biochem, 22:752-757



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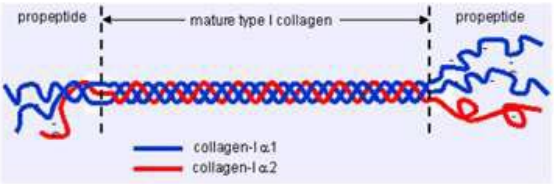
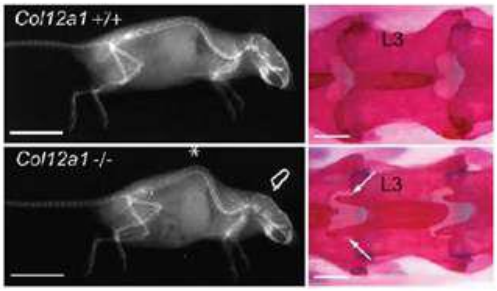
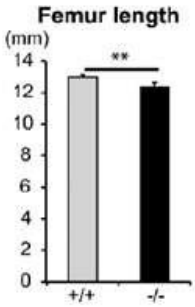
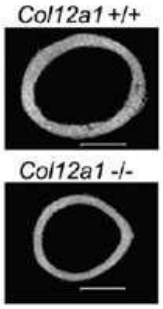
Collagen type I alpha 1 (COL1A1)
Functions

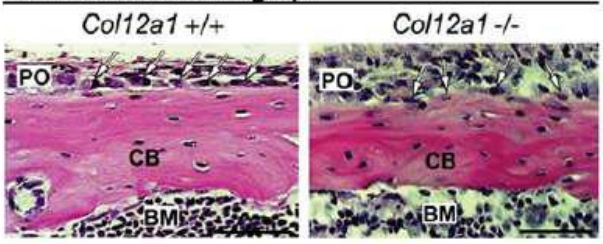




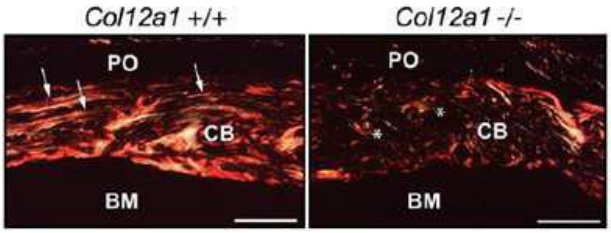


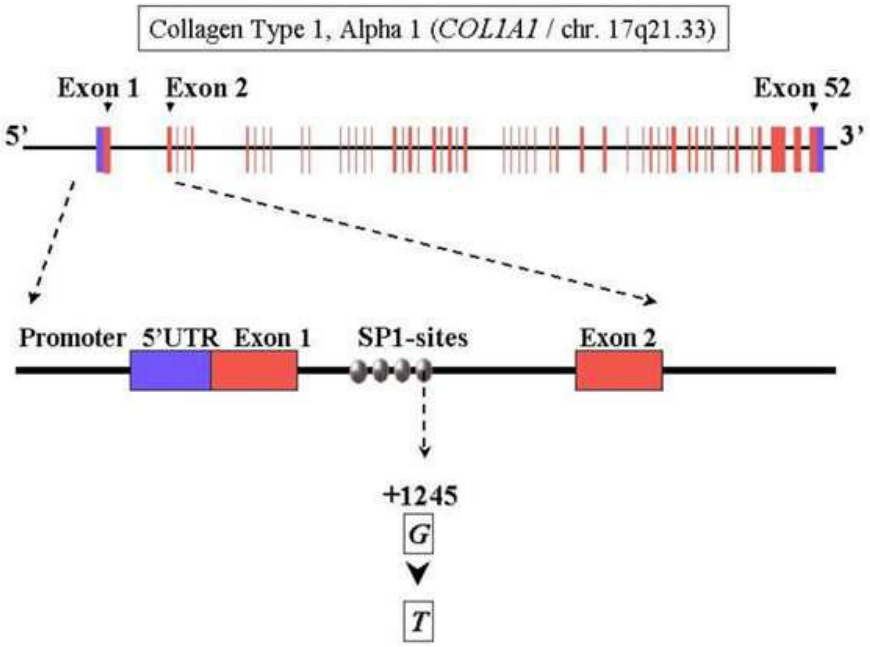


H & E stained micrograph



Polarized light micrograph



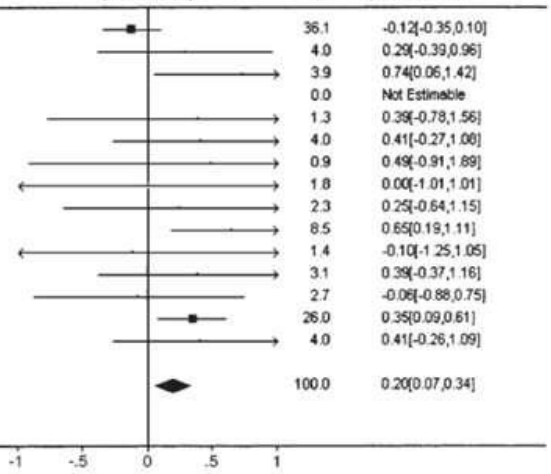

Collagen Type 1, Alpha 1 (COL1A1 / chr. 17q21.33)
Exon 1
Exon 2
Exon 52
5'
3'
Promoter
5'UTR
Exon 1
SP1-sites
Exon 2
+1245
G
T

A COL1A1 Sp1 binding site polymorphism predispose to osteoporotic fracture by affecting bone density and quality.
(Mann et al, 2001)
J Clin Invest 107:899-907.

Comparison: 01 BMD and Genotype
Outcome: 02 LS BMD SS vs ss

Study	SS n	mean(sd)	ss n	mean(sd)	SMD (95%CI Fixed)	Weight %	SMD (95%CI Fixed)
Braga 2000	349	0.82(0.16)	98	0.84(0.18)		36.1	-0.12[-0.35,0.10]
Garnero 1998	134	1.01(0.10)	9	0.98(0.16)		4.0	0.29[-0.39,0.96]
Grant 1996a	124	0.88(0.19)	9	0.74(0.16)		3.9	0.74[0.06,1.42]
x Grant 1996b	63	0.85(0.07)	1	0.82(0.00)		0.0	Not Estimable
Hampson 1998	47	1.13(0.15)	3	1.07(0.17)		1.3	0.39[-0.78,1.56]
Harris 2000	155	1.16(0.25)	9	1.06(0.12)		4.0	0.41[-0.27,1.08]
Heegard 2000	94	0.80(0.10)	2	0.75(0.16)		0.9	0.49[-0.91,1.89]
Hustmyer 1999	58	1.19(0.13)	4	1.19(0.11)		1.8	0.00[-1.01,1.01]
Keen 1999	113	0.96(0.16)	5	0.92(0.09)		2.3	0.25[-0.64,1.15]
Langdahl 1998	214	0.85(0.22)	20	0.71(0.13)		8.5	0.65[0.19,1.11]
Liden 1998	93	0.89(0.19)	3	0.91(0.21)		1.4	-0.10[-1.25,1.05]
McGuigan 2000	124	0.77(0.15)	7	0.71(0.19)		3.1	0.39[-0.37,1.16]
Sowers 1999	172	1.29(0.16)	6	1.30(0.15)		2.7	-0.06[-0.88,0.75]
Uitterlinden 1998a	1194	1.03(0.17)	58	0.97(0.19)		26.0	0.35[0.09,0.61]
Weichetova 2000	173	0.87(0.12)	9	0.82(0.12)		4.0	0.41[-0.26,1.09]
Total(95%CI)	3107		243			100.0	0.20[0.07,0.34]

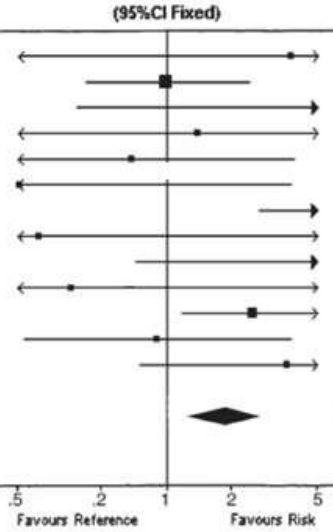
Test for heterogeneity chi-square=17.37 df=13 p=0.18
Test for overall effect z=2.92 p=0.004



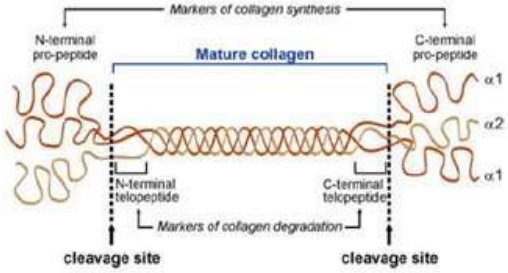
Comparison: 02 Fracture and Genotype
Outcome: 02 Fracture SS vs ss

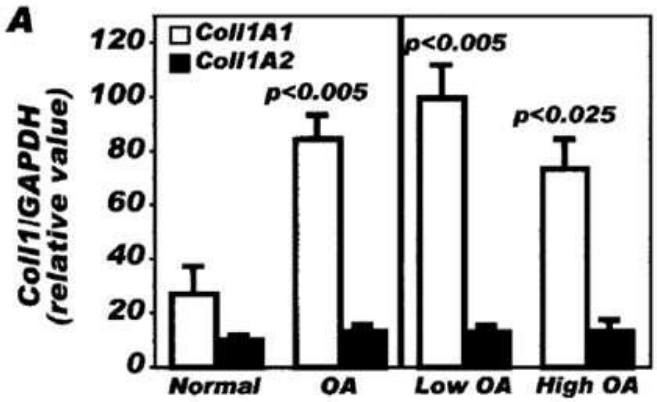
Study	Cases n/N	Controls n/N	OR (95%CI Fixed)	Weight %	OR (95%CI Fixed)
Alvarez 1999	1 / 20	0 / 24		1.2	3.77[0.15,97.74]
Braga 2000	6 / 44	92 / 671		26.8	0.99[0.41,2.42]
Grant 1996a	3 / 55	0 / 55		1.3	7.40[0.37,146.74]
Heegard 2000	0 / 16	2 / 117		1.7	1.40[0.06,30.46]
Hustmyer 1999	2 / 56	4 / 78		8.8	0.69[0.12,3.88]
Keen 1999	0 / 55	5 / 130		9.0	0.21[0.01,3.78]
Langdahl 1998	15 / 105	2 / 144		4.0	11.83[2.64,52.97]
Liden 1998	0 / 36	3 / 67		6.7	0.25[0.01,5.02]
McGuigan 2000	6 / 93	1 / 88		2.6	6.00[0.71,50.88]
Roux 1998	0 / 50	4 / 167		5.7	0.36[0.02,6.80]
Ulterlinden 1998a	8 / 111	50 / 1667		15.9	2.51[1.16,5.44]
Ulterlinden 1998b	2 / 74	42 / 1399		11.3	0.90[0.21,3.78]
Weichetova 2000	7 / 126	2 / 126		5.2	3.65[0.74,17.91]
Total(95%CI)	50 / 841	207 / 4733		100.0	1.86[1.28,2.70]

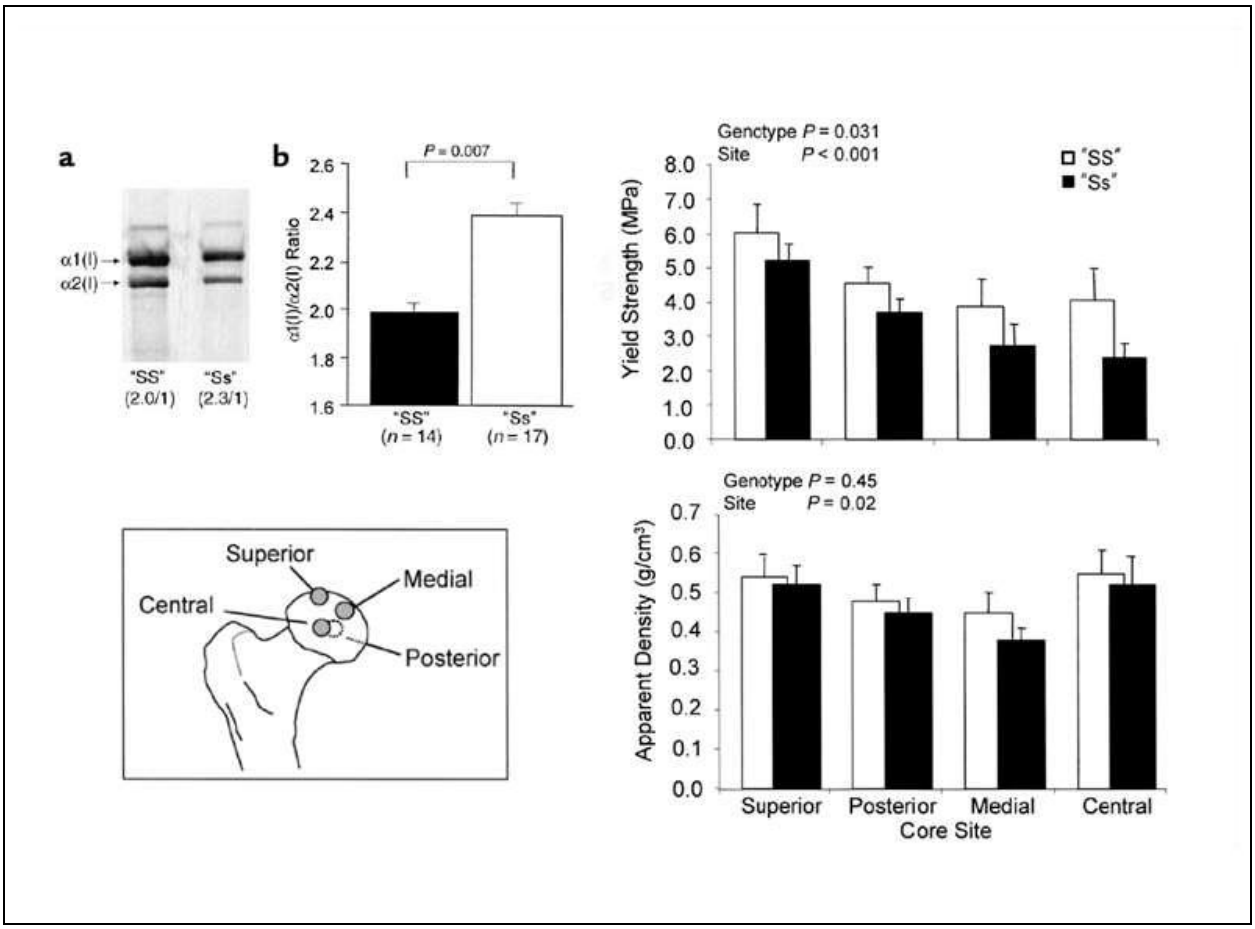
Test for heterogeneity chi-square=18.60 df=12 p=0.099
Test for overall effect z=3.26 p=0.001



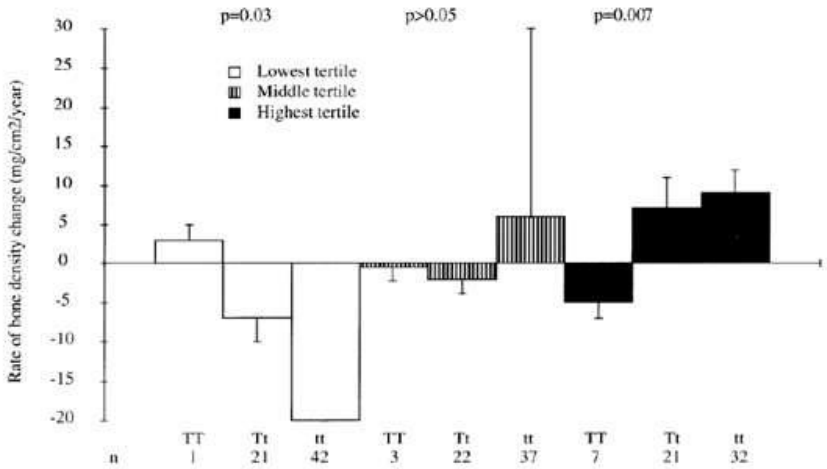
Altered mineralization of human osteoarthritic osteoblast is attributable to abnormal type I collagen production
(Couchourel et al, 2009)
Arthritis & Rheumatism, 60:1438-1450






a
α1(I)
α2(I)
"SS"
(2.0/1)
"Ss"
(2.3/1)
b
P = 0.007
α1(I)/α2(I) Ratio
2.6
2.4
2.2
2.0
1.8
1.6
"SS"
(n = 14)
"Ss"
(n = 17)
Genotype P = 0.031
Site P < 0.001
"SS"
"Ss"
Yield Strength (MPa)
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Superior
Medial
Central
Posterior
Genotype P = 0.45
Site P = 0.02
Apparent Density (g/cm³)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Superior
Posterior
Medial
Central
Core Site

Genetic control of bone density and turnover: role of the collagen 1α1, estrogen receptor, and vitamin D receptor genes
(Brown et al, 2001)
J Bone Miner Res 16:758-764



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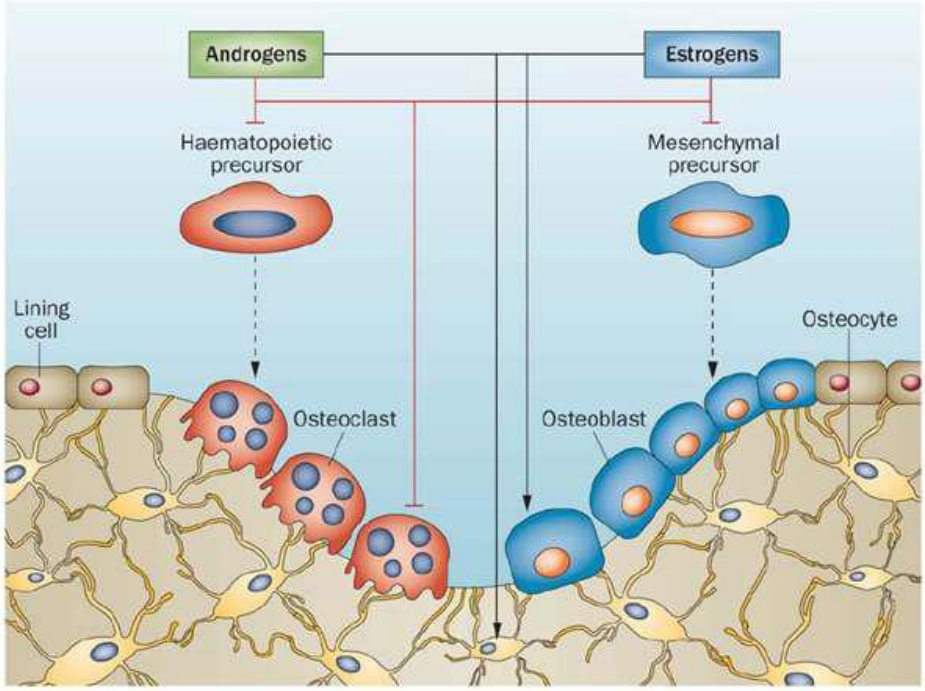
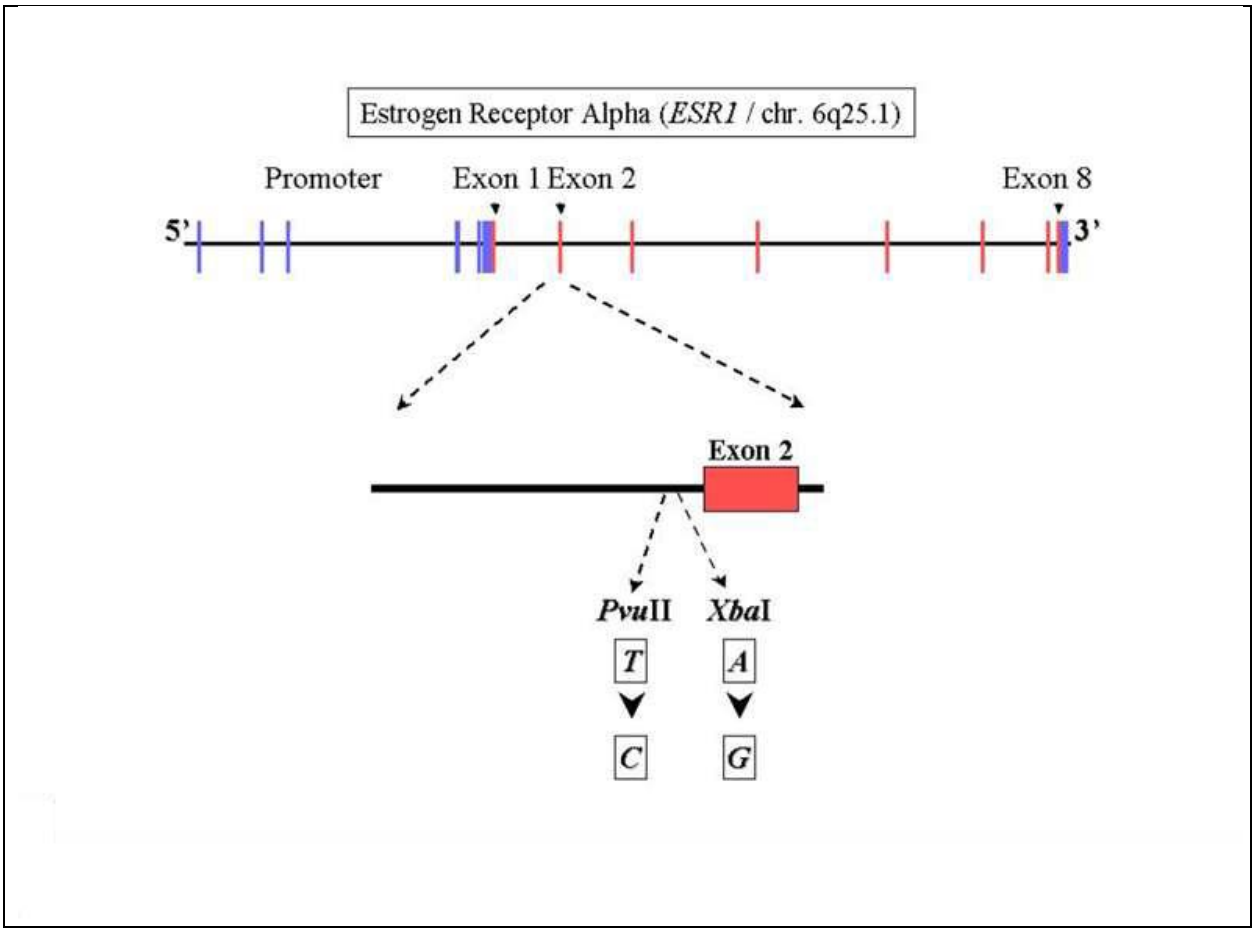
Role of estrogens in bone formation

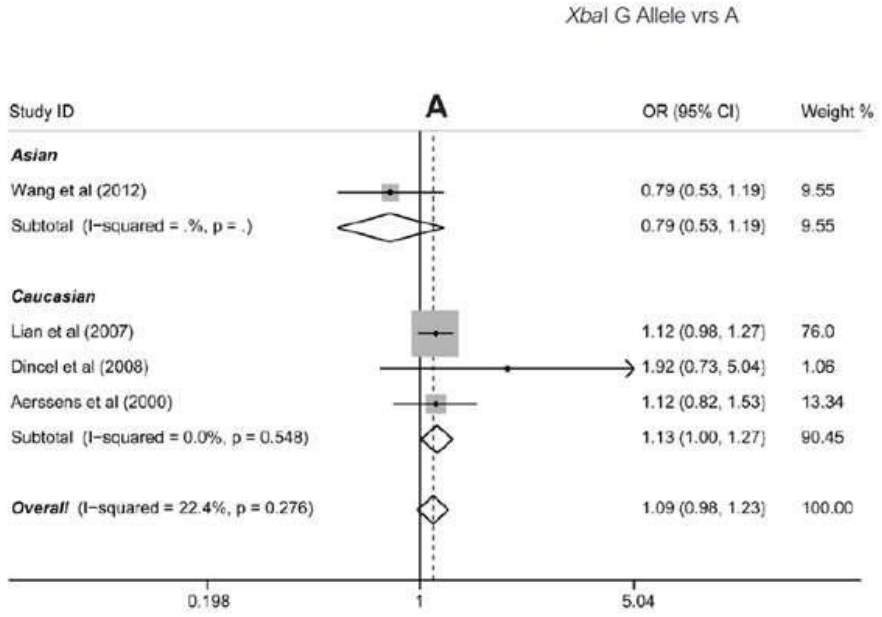



Estrogen Receptor Alpha (ESR1 / chr. 6q25.1)
Promoter
Exon 1
Exon 2
Exon 8
5'
3'
Exon 2
PvuII
XbaI
T
A
C
G

Association between estrogen receptor alpha gene (ESR1) PvuII (C/T) and XbaI (A/G) polymorphism and hip fracture risk: Evidece from a meta-analysis

(Tang et al, 2013)

Plos One 8:e82806

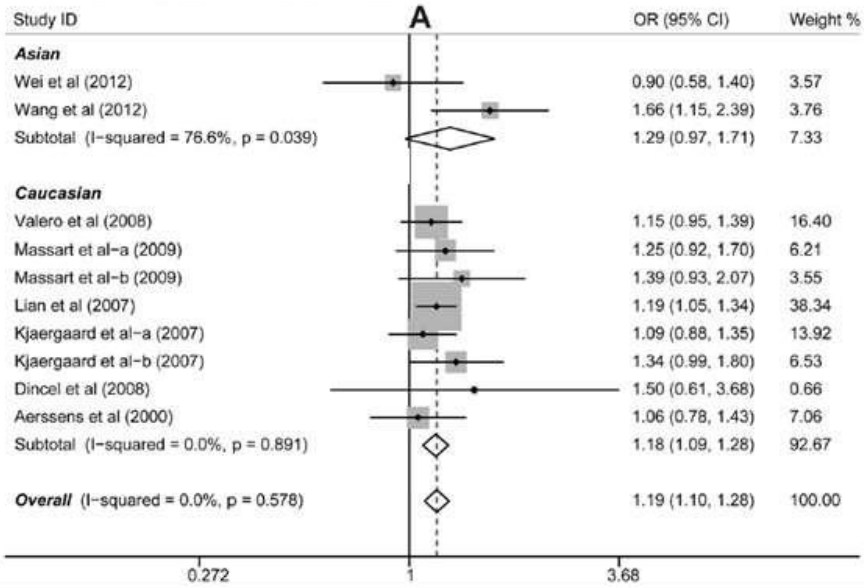


Association between estrogen receptor alpha gene (ESR1) PvuII (C/T) and XbaI (A/G) polymorphism and hip fracture risk: Evidece from a meta-analysis

(Tang et al, 2013)

Plos One 8:e82806

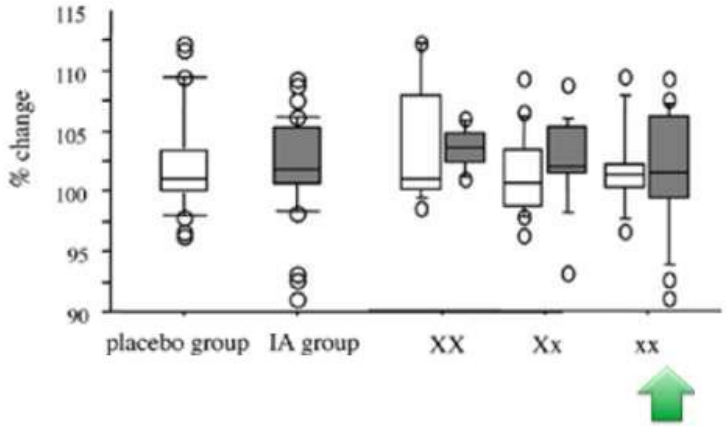
*Pvu*II
Alelo T vrs C



Alterations in bone turnover by isoflavone aglycone supplementation in relation to estrogen receptor α polymorphism.
(Katsuyama et al, 2010)
Molecular medicine reports: 3:531-535.

30 mg/day isoflavones supplement during 3 months

XbaI

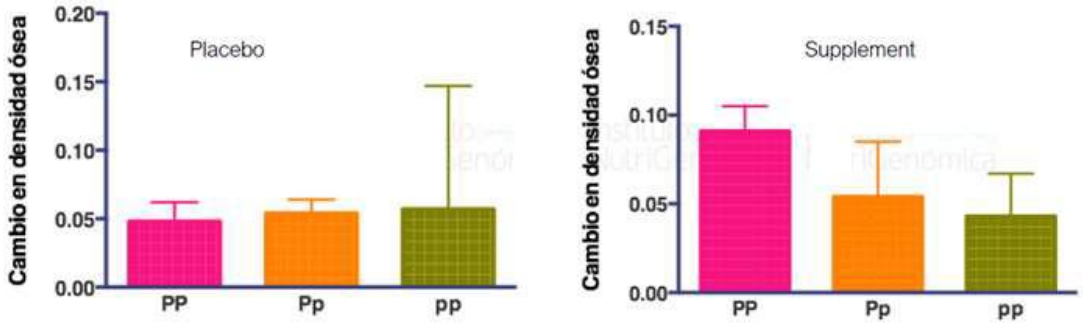


Association of estrogen receptor-α gene PvuII polymorphisms with the effect of calcium supplementation on skeletal development in chinese pubertal girls

(Yang et al, 2009)

Biomed Environ Sci 22:480-487.

Twelve-month daily supplement of 250 mg calcium carbonate and 60 IU vitamin D



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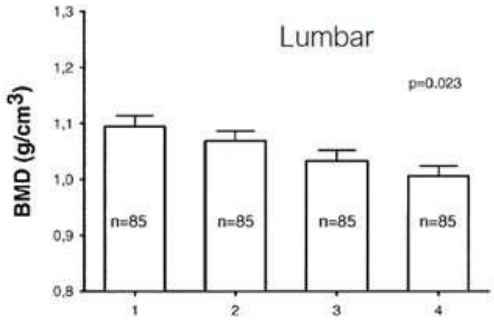
Does serum cholesterol contribute to vertebral bone loss in postmenopausal women?

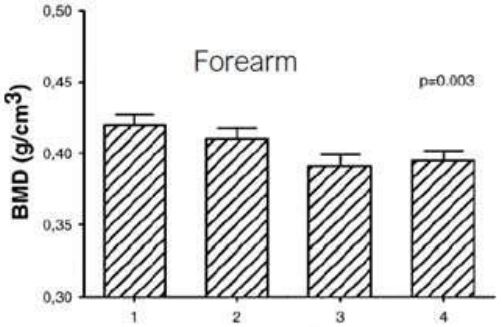
(Tanko et al, 2003)

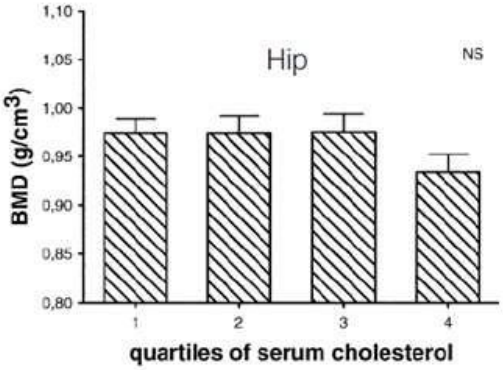
Bone 32:8-14

Total Cholesterol

Q1: 193 mg/dL
Q2: 232 mg/dL
Q3: 265 mg/dL
Q4: 310 mg/dL





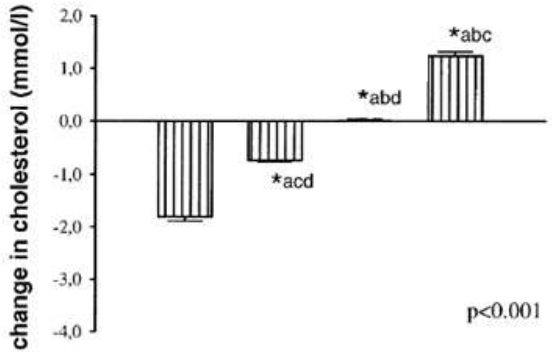


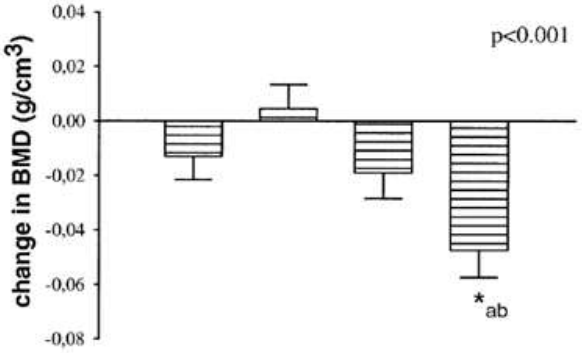
Does serum cholesterol contribute to vertebral bone loss in postmenopausal women?

(Tanko et al, 2003)

Bone 32:8-14

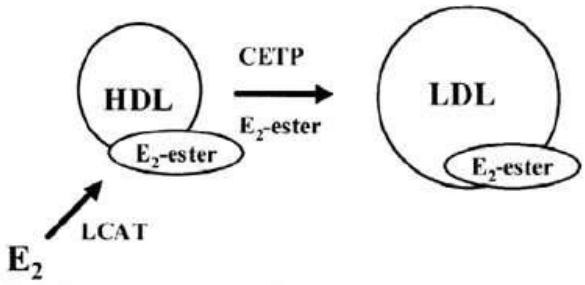
Eight years of follow-up…





HDL cholesterol and bone mineral density: Is there a genetic link?
(Ackert-Bicknell, 2012)
Bone 50:525-533

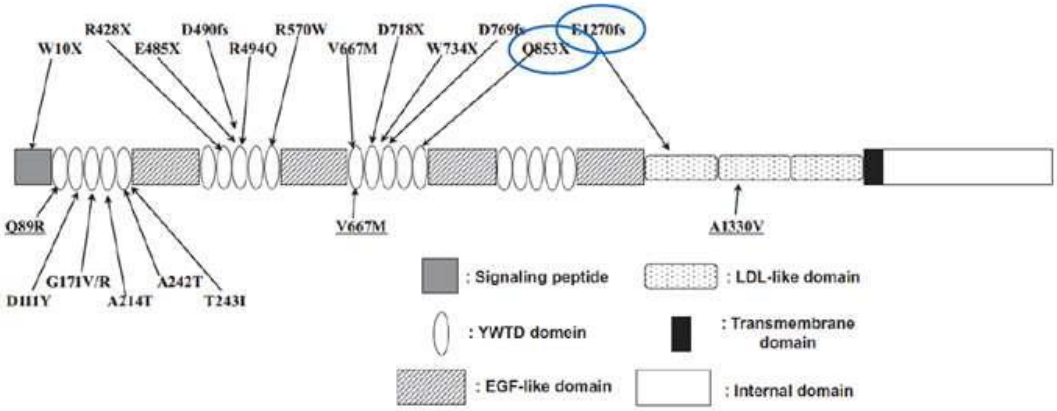
Gene	Name
ABCG8	ATP-binding cassette, sub-family G, member 8
APOE	Apolipoprotein E
ESR1	Estrogen receptor 1 (alpha)
GHRH	Growth hormone releasing hormone
IL6	Interleukin 6
MTHFR	5,10 methylenetetrahydrofolate reductase
PON1	Paraoxonase 1
PPARG	Peroxisome proliferator activated receptor gamma
TNF	Tumor necrosis factor



LDL Receptor-Related Protein 5 (LRP5) affects bone accrual and eye development

(Gong et al, 2001)

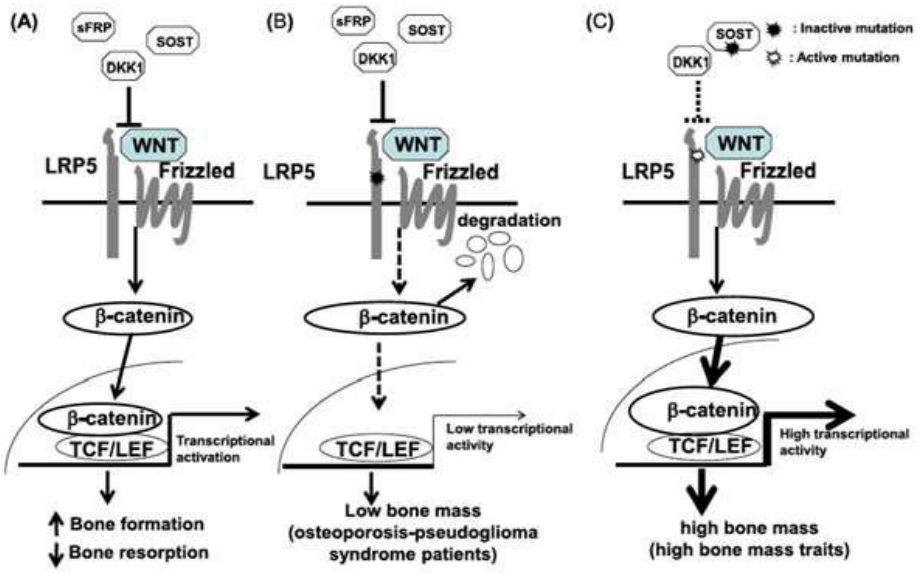
Cell 107:513-523



Genetics of osteoporosis

(Urano & Inoue, 2014)

Biochem Biophys Res Comm 452:287-293



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The NEW ENGLAND JOURNAL of MEDICINE

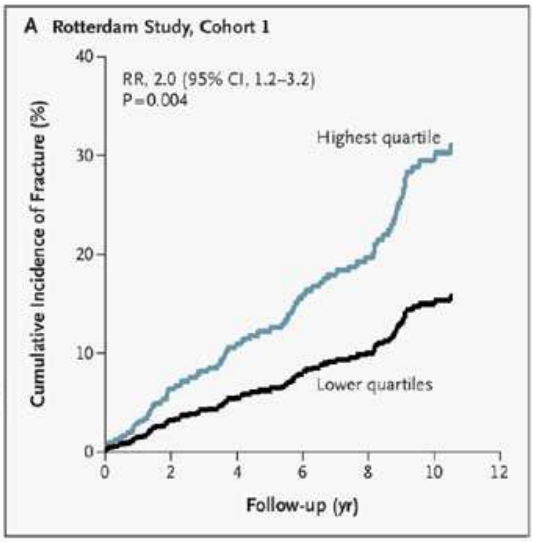
ESTABLISHED IN 1812 MAY 13, 2004 VOL. 350 NO. 20

Homocysteine Levels and the Risk of Osteoporotic Fracture

Joyce B.J. van Meurs, Ph.D., Rosalie A.M. Dhonukshe-Rutten, M.Sc., Saskia M.F. Pluijm, Ph.D., Marjolein van der Klift, M.D., Ph.D., Robert de Jonge, Ph.D., Jan Lindemans, Ph.D., Lisette C.P.G.M. de Groot, Ph.D., Albert Hofman, M.D., Ph.D., Jacqueline C.M. Witteman, Ph.D., Johannes P.T.M. van Leeuwen, Ph.D., Monique M.B. Breteler, M.D., Ph.D., Paul Lips, M.D., Ph.D., Huibert A.P. Pols, M.D., Ph.D., and André G. Uitterlinden, Ph.D.

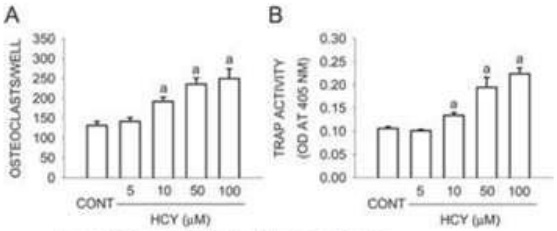
Table 4. Relative Risks and Population Attributable Risks for Independent Risk Factors for Incident Fracture.*

Factor	Relative Risk (95% CI)	Population Attributable Risk (95% CI)
		%
Age >75 yr	2.3 (1.7–3.1)	31 (25–48)
BMD, lowest quartile	1.6 (1.1–2.3)	13 (2–25)
Current smoker	1.6 (1.1–2.3)	10 (4–23)
Fall in previous year†	1.9 (1.2–2.7)	20 (10–35)
Dementia and cognitive impairment†	2.5 (1.5–4.1)	15 (7–30)
Homocysteine level, highest quartile	1.9 (1.4–2.6)	19 (10–29)



Homocysteine Enhances Bone Resorption by Stimulation of Osteoclast Formation and Activity Through Increased Intracellular ROS Generation

Jung-Min Koh,[1,2] Young-Sun Lee,[2,3] Yang Soon Kim,[3] Duk Jae Kim,[1] Hong-Hee Kim,[4] Joong-Yeol Park,[1] Ki-Up Lee,[1] and Ghi Su Kim[1]



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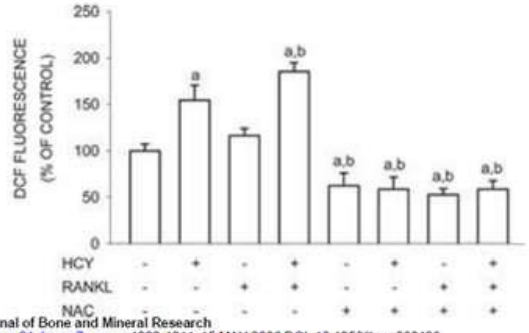
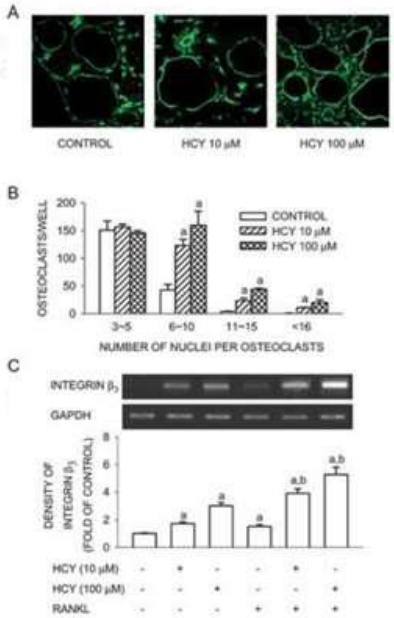


Journal of Bone and Mineral Research
Volume 21, Issue 7, pages 1003-1011, 15 MAY 2006 DOI: 10.1359/jbmr.060406
http://onlinelibrary.wiley.com/doi/10.1359/jbmr.060406/full#fig4

Homocysteine Enhances Bone Resorption by Stimulation of Osteoclast Formation and Activity Through Increased Intracellular ROS Generation

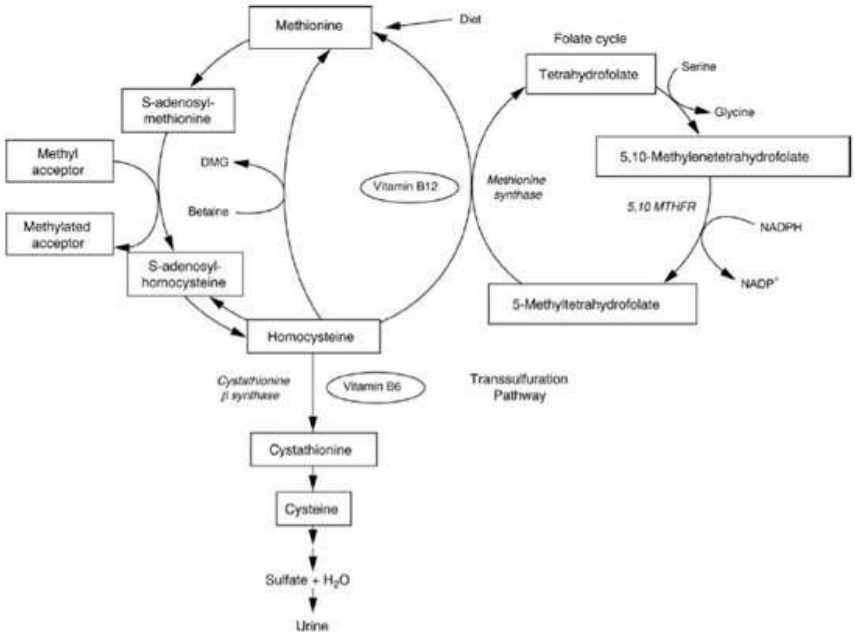


A candidate genetic risk factor for vascular disease: a common mutation in methylenetetrahydrofolate reductase
(Frosst et al, 1995)
Nat Genet 10:111-113

Table 1 Correlation between MTHFR genotype and enzyme activity, thermolability and plasma homocysteine level

	Genotype		
	−/−	+/−	+/+
	n=19	n=9	n=12
Specific activity[a,b] (nmol CH_2O/mg protein/hr)	22.9±1.7 (11.8–33.8)	15.0±0.8 (10.2–18.8)	6.9±0.6 (2.6–10.2)
Residual activity after heating[a,b] (%)	66.8±1.5 (55–76)	56.2±2.8 (41–67)	21.8±2.8 (10–35)
Plasma homocysteine[a,c] (μM)(after fasting)	12.6±1.1 (7–21)	13.8±1.0 (9.6–20)	22.4±2.9 (9.6–42)
Plasma homocysteine[a,c] (μM)(post-methionine load)	41.3±5.0[d] (20.9–110)	41±2.8 (29.1–54)	72.6±11.7[e] (24.4–159)

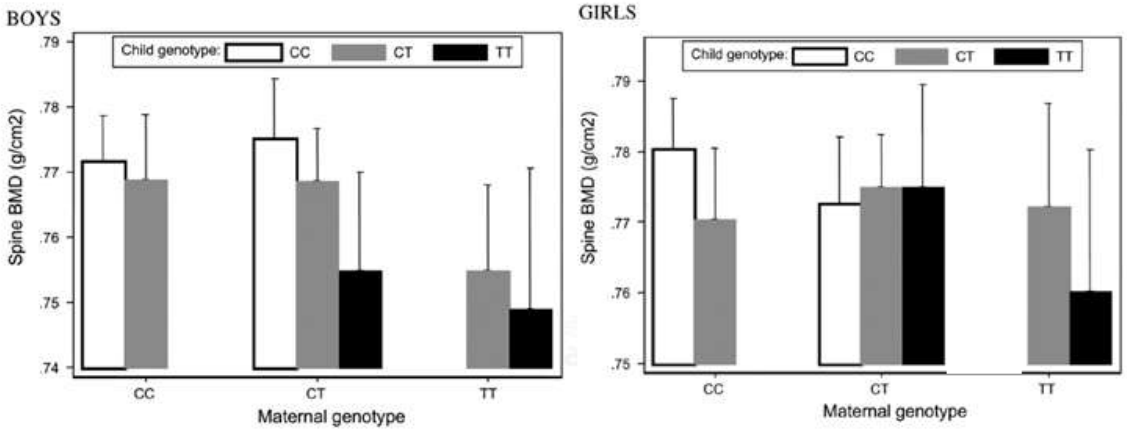
B vitamins and osteoporosis



Insights into the programming of bone development from the Avon Longitudinal Study of Parents and Children (ALSPAC)

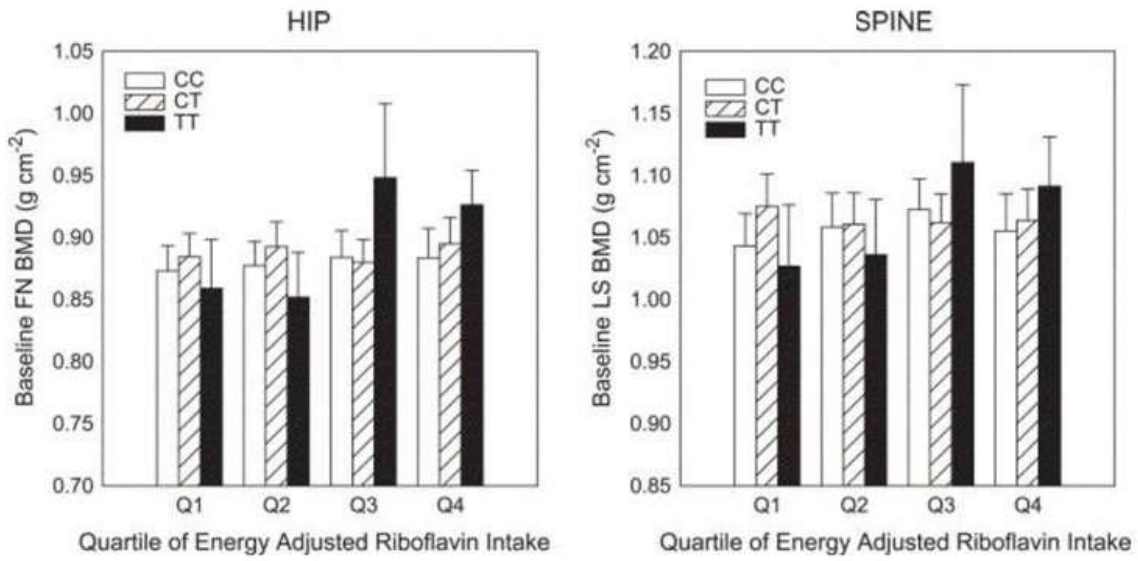
(Steer & Tobias, 2011)

Am J Clin Nutr 94(6 Suppl):1861S-1864S



Mean (95% CI) spine bone mineral density (BMD) for mother-child combinations of MTHFR C677T genotype adjusted for child age, height, and weight for boys and girls separately (n = 1015 and 997, respectively).

Methylenetetrahydrofolate reductase polymorphism interacts with riboflavin intake to influence bone mineral density
(McDonald et al, 2004)
Bone 35:957-964



Marked decreased in plasma antioxidants in aged osteoporotic women: results of a cross-sectional study
(Maggio et al, 2003)
J Clin Endocrinol Metab 88:1523-1527

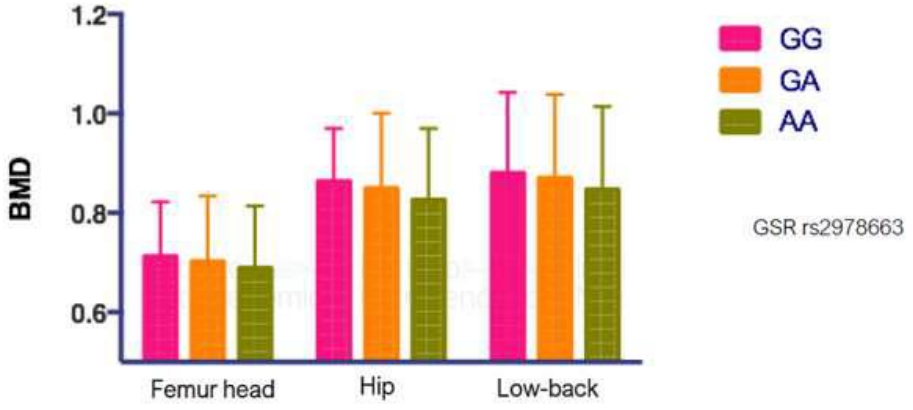
	Osteoporotics	Controls
Plasma vitamin C (mmol/liter)	30 ± 3,7	55,5 ± 13,1
Plasma vitamin E (mmol/liter)	46,7 ± 5	62,8 ± 8,76
Plasma SOD (U/ml)	24,22 ± 3,8	31,38 ± 3,1
MDA (malondialdehyde) (mmol/liter)	1,13 ± 0,54	0,77 ± 0,35
NO (Nitric oxide) (mmol Hb)	0,33 ± 0,24	0,21 ± 0,13

Role of antioxidant systems, lipid peroxidation, and nitric oxide in postmenopausal osteoporosis
(Ozgocmen et al, 2006)
Mol Cell Biochem 295:45-52

Antioxidant enzymes GSR, SOD1, SOD2, and CAT gene variants and bone mineral density values in postmenopausal women: a genetic association analysis

(Jurkovic et al, 2012)

Menopause 19:368-376



Conclusions

1. Osteoporosis heritability is evident from a very early age.
2. In the case of risk alleles, the best treatment seems to be calcium and vitamin D supplementation.
3. Some other compounds such as soy isoflavones could contribute to increase vitamin D levels.
4. There are other associated factors such as the lipid metabolism and antioxidative status, which may influence the development of osteoporosis.

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What is metabolic syndrome?

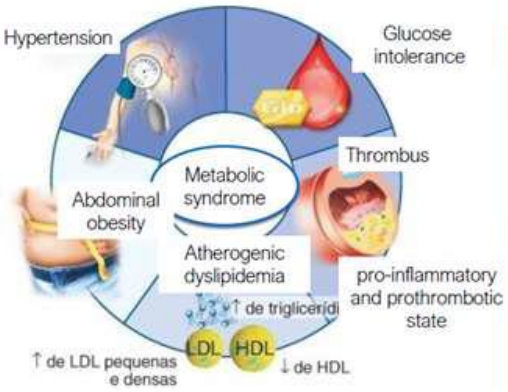


Table 3. Diagnostic criteria according to WHO (1999)

Presence of diabetes mellitus, disturbed glucose, impaired glucose tolerance (glucose uptake < 25% after hyperinsulinemic-euglycemic clamp, as well as 2 or more of the following factors:
Body Mass Index > 30 and/or waste-to-hip ratio > 0,9 (men) or > 0,85 (women)
Triglycerides ≥ 150 mg/dl and/or cHDL < 35 mg/dl (men) or < 39 mg/dl (women
Blood pressure ≥ 140/90 mmHg
Microalbuminuria ≥ 20 µg/min or albumin / creatinine ≥ 30 mg/g
cHDL: High Density Lipoprotein Choesterol; WHO: World Health Organization.

Table 4. Diagnostic criteria according to emir (1999)

Presence of insulin resistance (basal > 75 percentile), in non-diabetic population, as well as 2 or more of the following factors:Waist circumference ≥ 94 cm (men) or ≥ 80 cm (women)
Triglycerides ≥ 175 mg/dl or cHDL < 40 mg/dl or specific treatment
Blood pressure ≥ 140/90 mmHg or specific treatment
Basal blood glucose ≥ 110 mg/dl (no diabetes)
cHDL: High Density Lipoprotein Choesterol; EGIR: European Group of Insulin Resistance.

Table 5. Diagnostic criteria according to ATPIII (2001)

Presence of 3 or more of the following factors:
Waist circumference > 102 cm (men) or > 88 cm (women)
Triglycerides ≥ 150 mg/dl
cHDL < 40 mg/dl (women) or < 50 mg/dl (women)
Blood pressure ≥ 130/85 mmHg
Basal blood glucose ≥ 110 mg/dl

ATPIII: Adult Treatment Panel; cHDL: High Density Lipoprotein Choesterol.

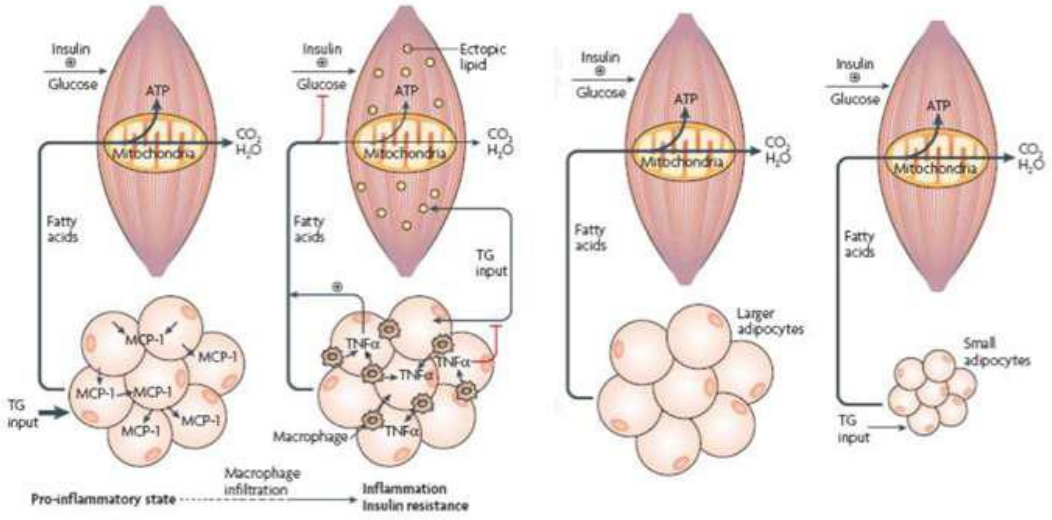
Table 6. Diagnostic criteria according to AACE
Medical history

Cadiovascular desease diagnosis, hypertension, polycystic ovary, non-alcoholic fatty liver or acanthosis nigricans.
Family history of type 2 diabetes, hypertension or cardiovascular disease
History of gestational diabetes or glucidic intolerance
Non-Caucasian race
Sedentary lifestyle
Age > 40 years old
Altered parameters:
Body masss index ≥ 25 and /or waist > 102 cm (men) or 88 cm(women)
Triglycerides > 150 mg/dl
cHDL < 40 mg/dl (men) or 50 mg/dl (women)
Blood pressure > 130/85 mmHg
Basal blood glucose: 110-125 mg/dl or glucose 2 hours after oral glucose overload: 140-200 mg/dl (diabetes is excluded)
AACE: American Association of Clinical Endocrinologists; cHDL: High Density Lipoprotein Cholesterol.

Table 7. Diagnostic criteria according to IDF

Abdominal obesity (waist circumference ≥ 94 cm for European men and ≥ 80 cm for European women)*
Two or more of the following factors must also be fulfilled:
Triglycerides ≥150 mg/dl or specific treatment of this lipid alteration
cHDL < 40 mg/dl (men) or < 50 mg/dl (women) or specific treatment of this lipid alteration
Systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or treatment of previously diagnosed hypertension
Basal blood pressure ≥ 100 mg/dl or previously diagnosed type 2 diabetes
cHDL: High Density Lipoprotein Cholesterol; IDF: International Diabetes Federation
*Cut-off values for waist circumference vary depending to the ethnic group taking into consideration.

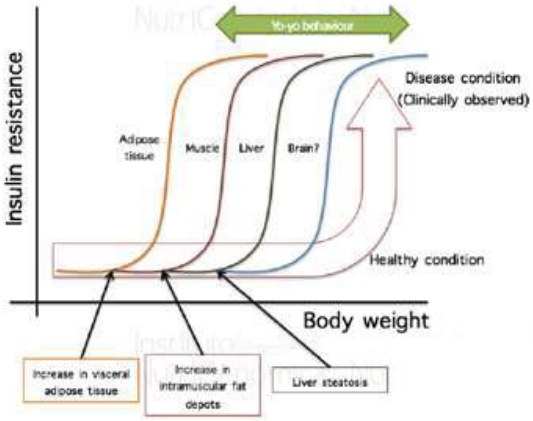
What is metabolic syndrome?

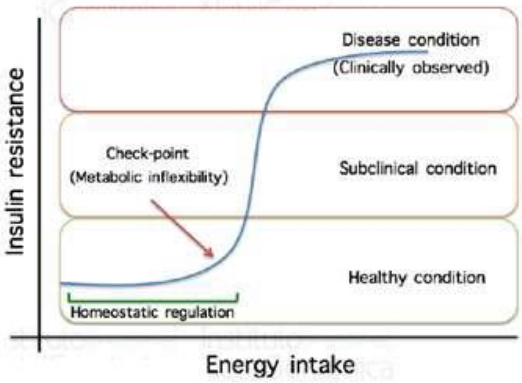


Effect of Dietary Bioactive Compounds on Mitochondrial and Metabolic Flexibility

(Serrano et al, 2016)

Diseases 4,14





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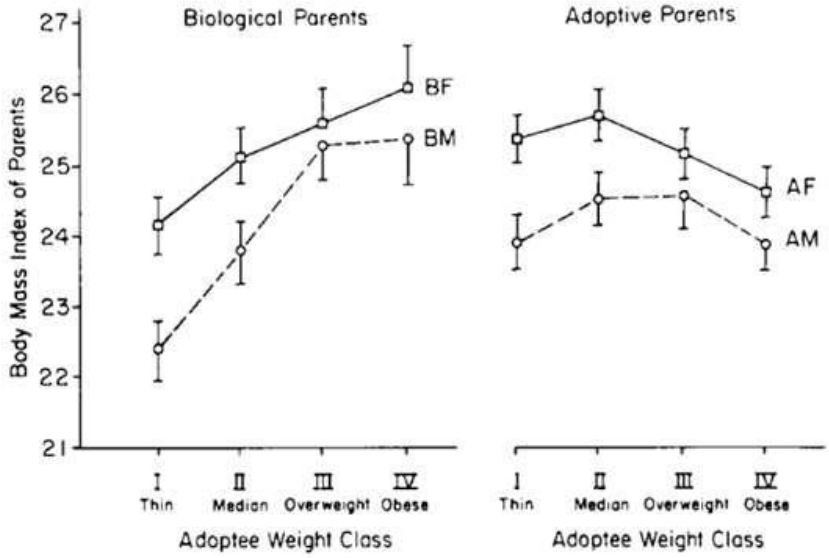
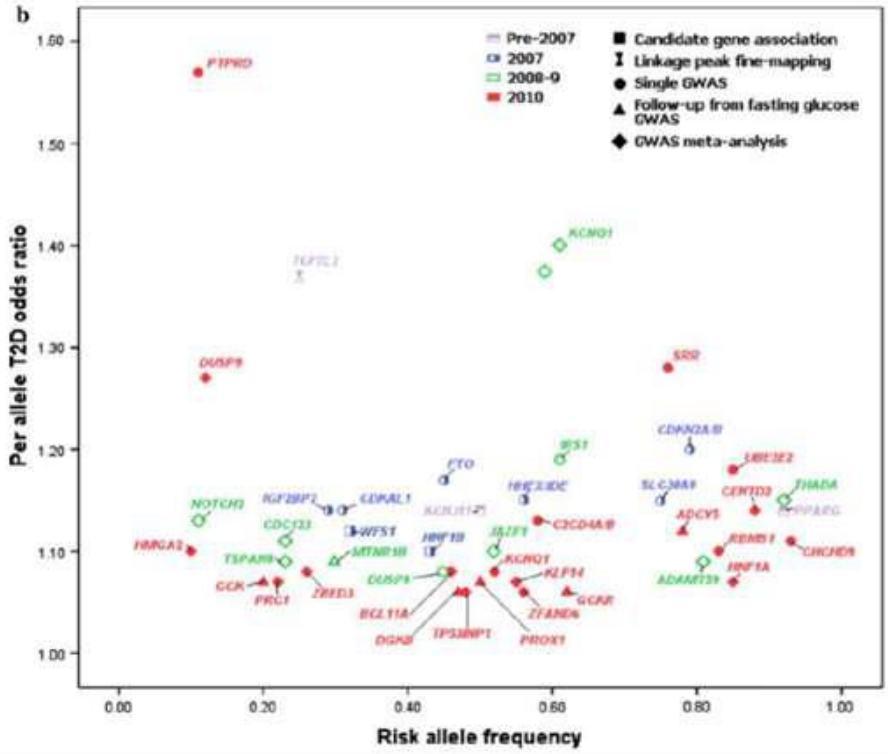
An adoption study of human obesity
(Stunkard et al, 1986)
N Engl J Med 314:193-198



Type 2 diabetes and obesity: genomics and the clinic

(Travers & McCarthy, 2011)

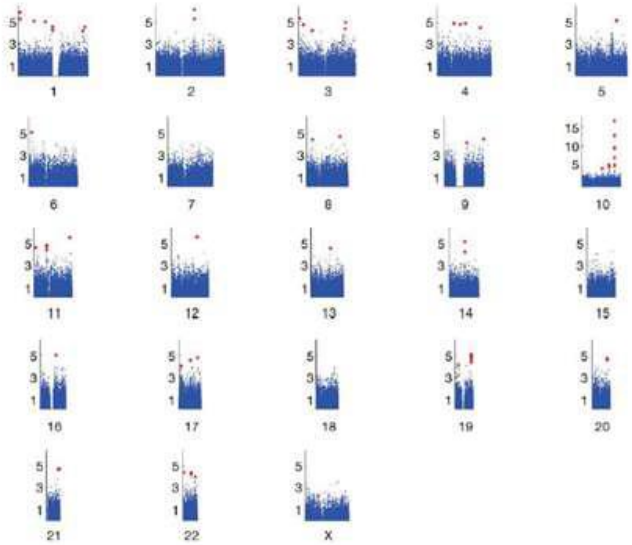
Hum Genet 130:41-58



A genome-wide association study identifies novel risk loci for type 2 diabetes

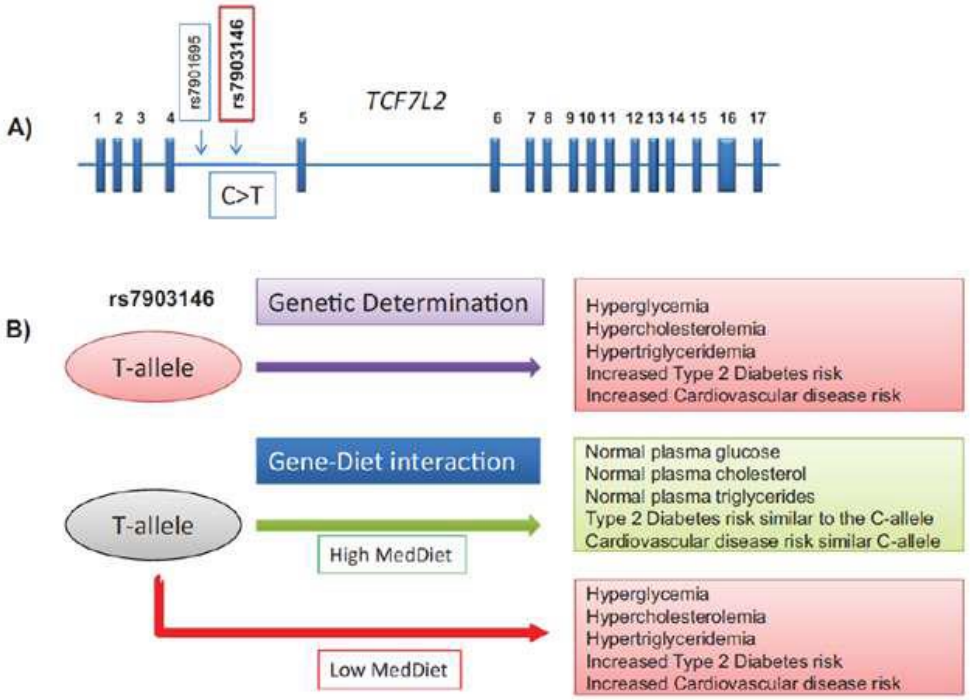
(Sladek et al, 2007)

Nature 445:881-885



Gene	SNP	Risk allele	Odds ratio
TCF7L2	rs7903146	T	2.77
SLC30A8	rs13266634	C	1.53
HHEX	rs1111875	G	1.44
HHEX	rs7923837	G	1.45
LOC387761	rs7480010	G	1.40
EXT2	rs3740878	A	1.46
EXT2	rs11037909	T	1.47
EXT2	rs1113132	C	1.36

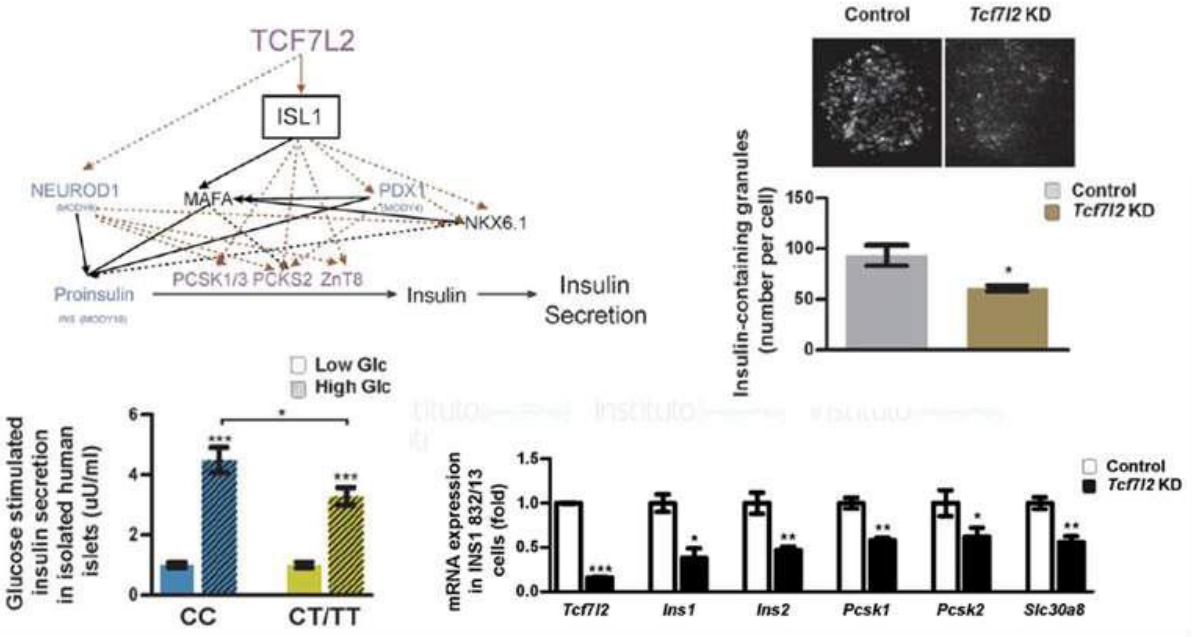
TCF7L2 Transcription factor 7 like 2



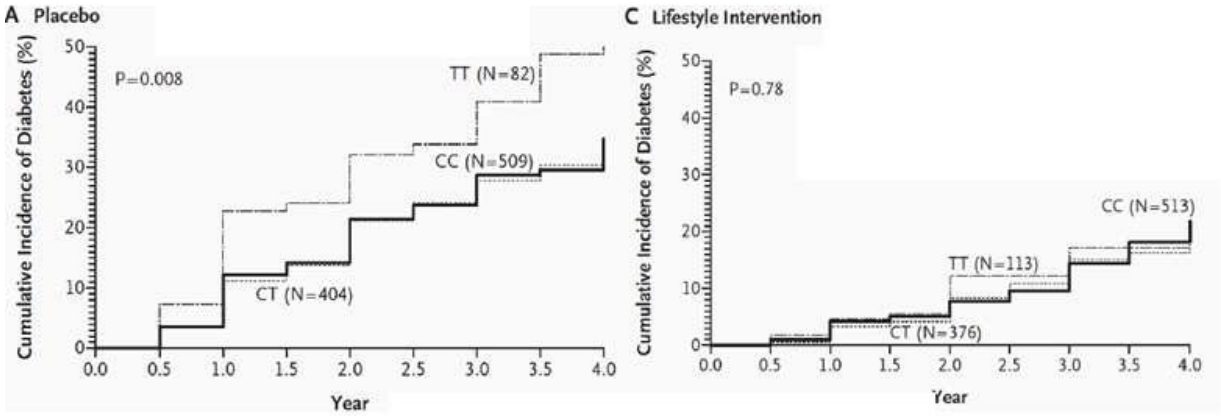
TCF7L2 is a master regulator of insulin production and processing

(Zhou et al, 2014)

Hum Mol Gen 23:6419-6431



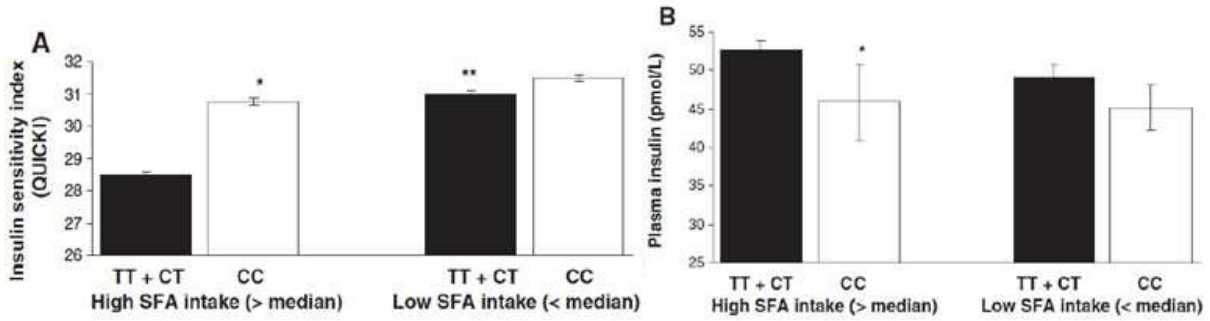
TCF7L2 Polymorphisms and Progression to Diabetes in the Diabetes Prevention Program
(Florez et al, 2006)
NEJM 355:241-250



Dietary saturated fat, gender and genetic variation at the TCF7L2 locus predict the development of metabolic syndrome

(Phillips et al, 2012)

J Nutr Biochem 23:239-244

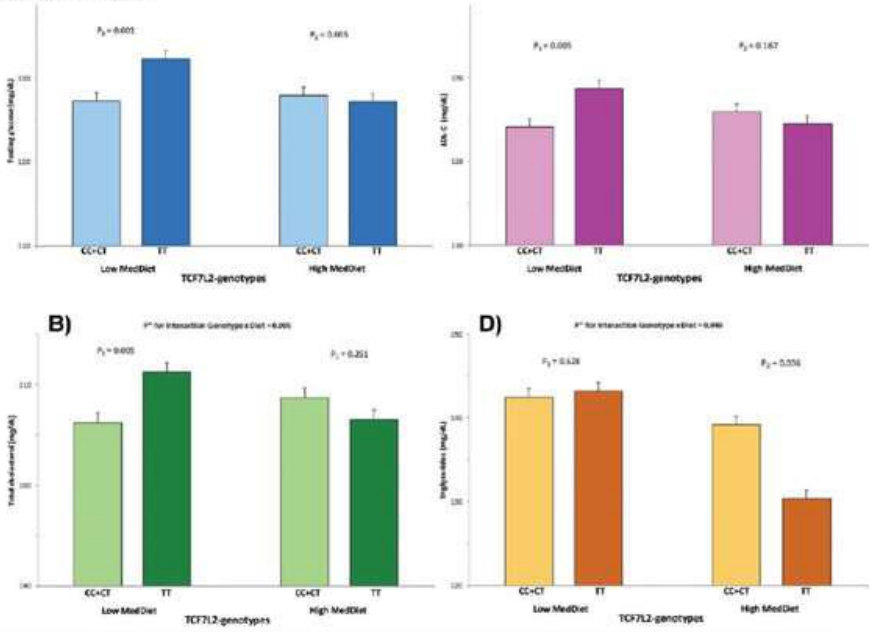


TCF7L2 rs7903146

Mediterranean diet reduces the adverse effect of the TCF7L2-rs7903146 polymorphism on cardiovascular risk factors and stroke incidence: a randomized controlled trial in a high-cardiovascular-risk population

(Corella et al, 2013)

Diabetes Care 36:3803-3811



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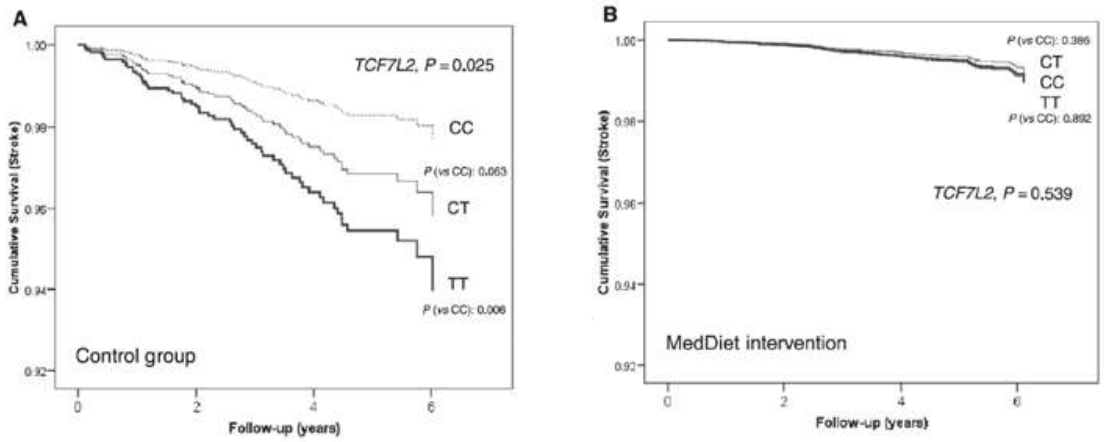
Diabetes Care 36:3803-3811



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General treatment objectives

Nutrition objectives

Anthropometric

1. Gradual and prolonged weight loss. A feasible weight loss objective could include reducing the total caloric intake by 100 kcal/day.
2. Improving waist-to-hip ratio.
3. Reducing body fat percentage (effects of fat atrophy)

Blood biochemistry

4. Improving total cholesterol levels, cholesterol/HDL ratio, triglyceride/HDL ratio and total cholesterol/HDL ratio; reducing triglyceride levels.
5. Lowering glucose and preprandial insulin levels to normal (improving insulin sensitivity).
6. Reducing inflammatory markers.
7. Reducing high blood pressure.

Lifestyle

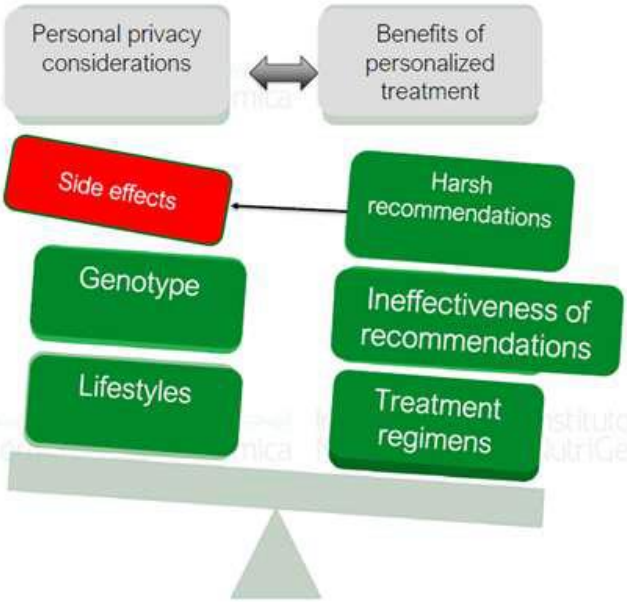
8. Encouraging an increase in physical activity.

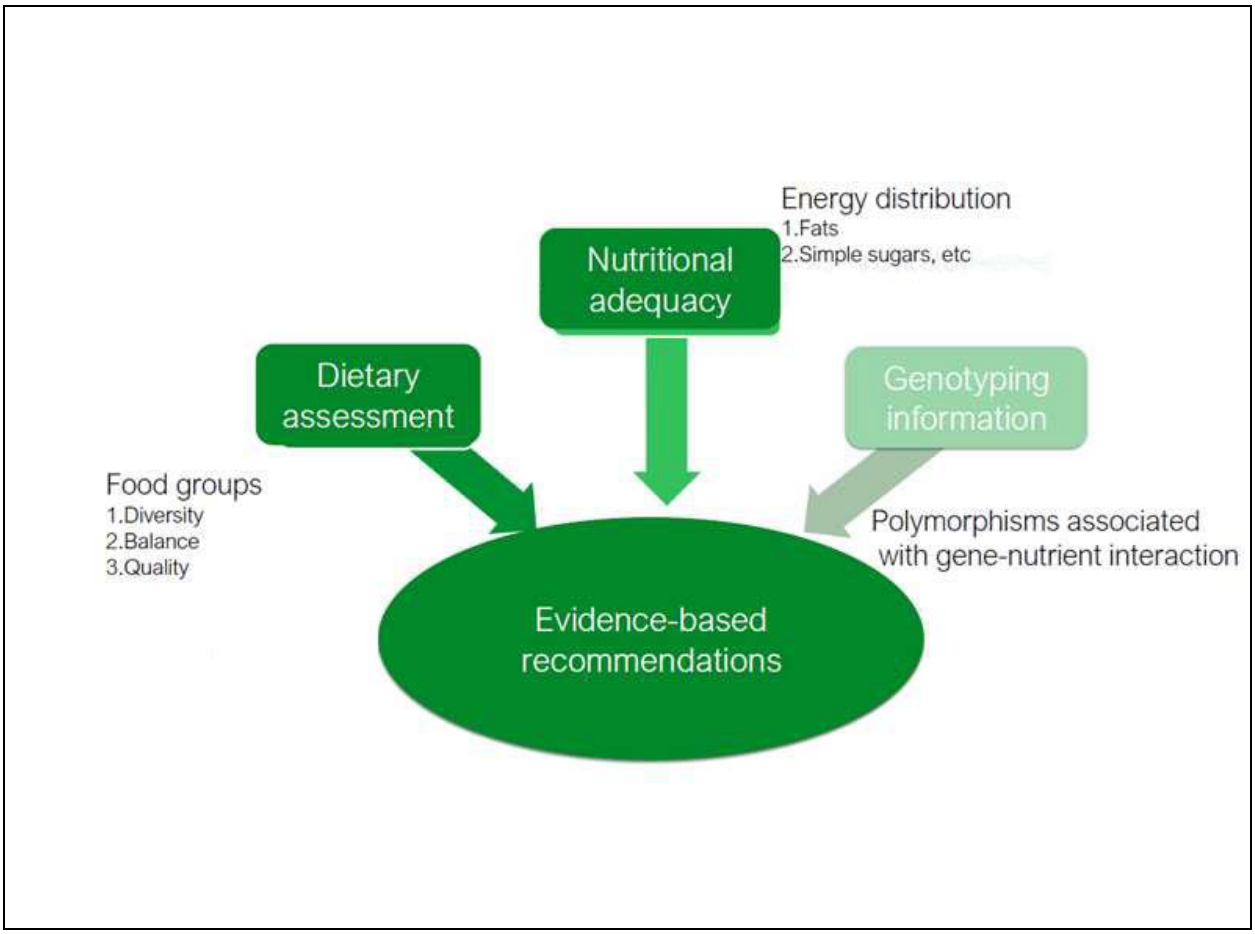
Objectives of nutritional treatments

	Carbohydrate % daily energy	Fat % daily energy	Protein % daily energy	Saturated Fat % daily energy	Monounsaturated Fat % daily energy	Poliunsaturated Fat % daily energy	Cholesterol mg/day	Fiber g/day	Sodium mg/day
United States Department of Agriculture	55-65	20-30	15	<10			<300	20-30	<2300
American Heart Association	50-60	25-35	15	<7			<300	25	<2400
National Colesterol Education Program Paso I	50-60	25-35	15	<10	20	10	<300	20-30	<2400
Dietary Approaches to Stop Hipertensión	50-60	25-35	15	<7				20-30	<1500
Therapeutic Life Style Changes	50-60	25-35	15	<7			<200	20-30	<2400
American Diabetes Association	55-65	20-30	15	<10			<300		
American Dietétic Association	55-65	20-30	15	<10			<300		
Dieta Mediterránea	55	30	15	<10	15	5	200	20	

1. Reducing fat intake
2. Saturated fats must not provide more than 7% of energy
3. Increasing monounsaturated fats intake
4. Simple sugars intake

Initial considerations….




Energy distribution
1.Fats
2.Simple sugars, etc
Nutritional adequacy
Dietary assessment
Genotyping information
Food groups
1.Diversity
2.Balance
3.Quality
Polymorphisms associated with gene-nutrient interaction
Evidence-based recommendations

Protocol recommendation for personalized treatment

Improved weight management using genetic information to personalize a calorie controlled diet

(Arkadianos et al, 2007)

Nutrition Journal 6:29

Gene	Gene symbol	Polymorphism
Angiotensin I converting enzyme	***ACE***	INS/DEL
Apolipoprotein C-III	***APOC3***	3175C>G
Cystathionine-beta-synthase	***CBS***	699C>T
Cholesteryl ester transfer protein	***CETP***	279G>A
Collagen, type I, alpha 1	***COL1A1***	G Sp1 T
Glutathione S-transferase M1	***GSTM1***	Deletion (*)
Glutathione S-transferase pi	***GSTP1***	313A>G 341C>T
Glutathione S-transferase theta 1	***GSTT1***	Deletion (*)
Interleukin 6	***IL6***	-174G>C -634G>C
Lipoprotein lipase	***LPL***	1595C>G
5-methyltetrahydrofolate-homocysteine methyltransferase reductase	***MTRR***	66A>G
5,10-methylenetetrahydrofolate reductase	***MTHFR***	1298A>C 677 C>T
5-methyltetrahydrofolate-homocysteine methyltransferase	***MTR***	2756A>G
Nitric oxide synthase 3 (endothelial cell)	***NOS3***	894G>T
Peroxisome proliferator-activated receptor gamma	***PPARG***	Pro12Ala
Superoxide dismutase 2, mitochondrial	***SOD2***	-28C>T
Superoxide dismutase 3, extracellular	***SOD3***	760C>G
Tumor necrosis factor	***TNFα***	-308G>A
Vitamin D receptor	***VDR***	C TaqI T T BsmI C T FokI C

Variations in MTHFR, MTRR, MTR, CBS

800 µg folic acid, 15 mg vitamin B6, 20 µg vitamin B12 supplementation

Variations in GSTMI, GSSTI, GSTPI

Regular servings of cruciferous vegetables (5 times a week) and garlic (daily).

Variations in SOD2, SOD3, NOS3

Vitamin A (5,000 IU), vitamin C (250 mg), vitamin E (200 IU) supplementation

Variations in VDR, COLIAI

Lowering coffee intake to less than 2 cups a day, increasing dairy products intake or 800 IU vitamin D and 1,300 mg calcium supplementation

Variations in TNFα, IL6, NOS3

700-1400 mg Omega-3 supplementation

Variations in CETP, LPL, APOC3

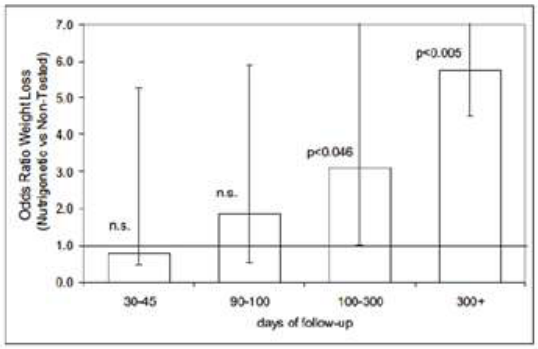
Reducing saturated fat intake and restricting dairy products intake

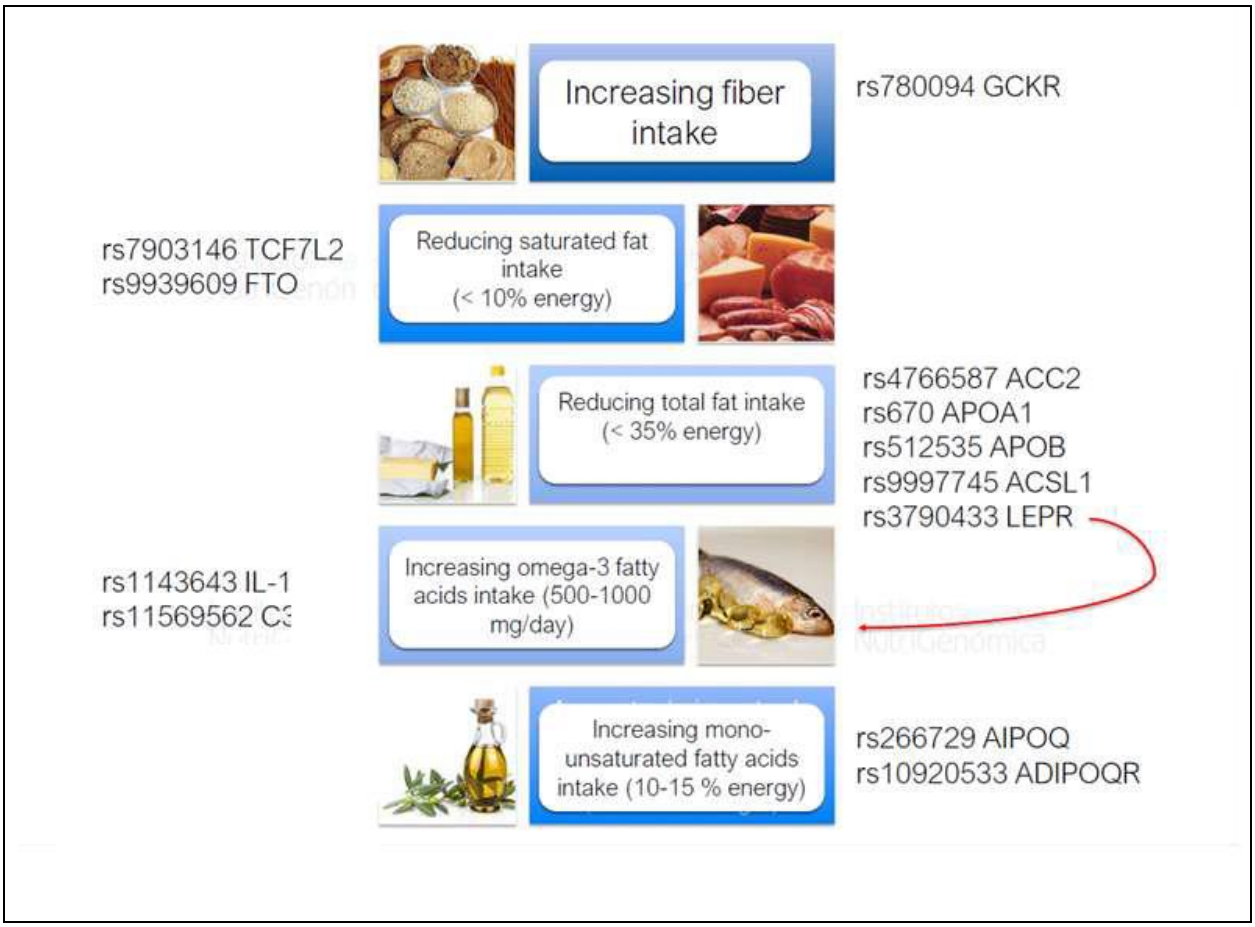
Variations in ACE, PPARG

Low-glycemic diet + exercise

Table 5: Weight and BMI loss (or gain if negative) in the two groups.

	Non tested group					Nutrigenetic group					P < *
Time point	**n**	**weight as % of baseline**	**Δ kg**	**Δ BMI (kg/m²)**	**% lost weight**	**n**	**weight as % of baseline**	**Δ kg**	**Δ BMI (kg/m²)**	**% lost weight**	
baseline	43	100.0%				50	100.0%				
30–45	35	95.4%	4.77	1.59	94.3%	40	96.3%	3.70	2.10	92.5%	0.50
90–100	23	92.2%	8.42	2.78	86.9%	26	93.4%	6.42	3.51	96.1%	0.64
100–300	36	93.4%	6.94	2.35	88.9%	44	92.9%	6.88	3.19	96.4%	0.29
> 300	22	103.2%	-2.74	-0.86	31.8%	26	95.6%	3.61	2.54	73.1%	**0.023**




Increasing fiber intake
rs780094 GCKR
rs7903146 TCF7L2
rs9939609 FTO
Reducing saturated fat intake (< 10% energy)
Reducing total fat intake (< 35% energy)
rs4766587 ACC2
rs670 APOA1
rs512535 APOB
rs9997745 ACSL1
rs3790433 LEPR
rs1143643 IL-1
rs11569562 C3
Increasing omega-3 fatty acids intake (500-1000 mg/day)
Increasing mono-unsaturated fatty acids intake (10-15 % energy)
rs266729 AIPOQ
rs10920533 ADIPOQR

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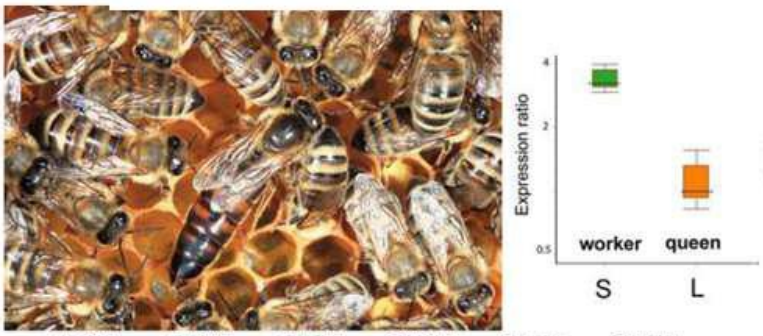
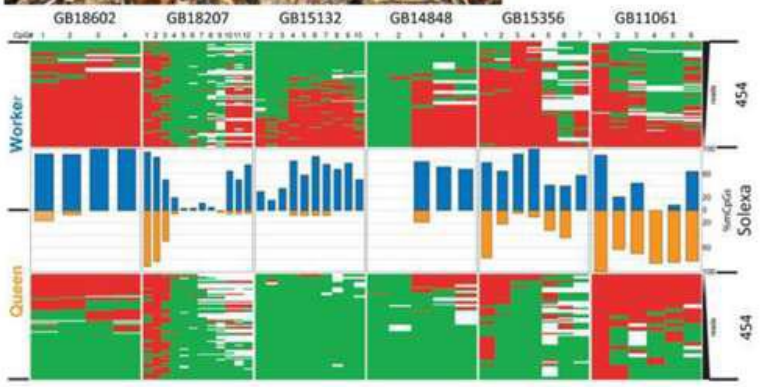
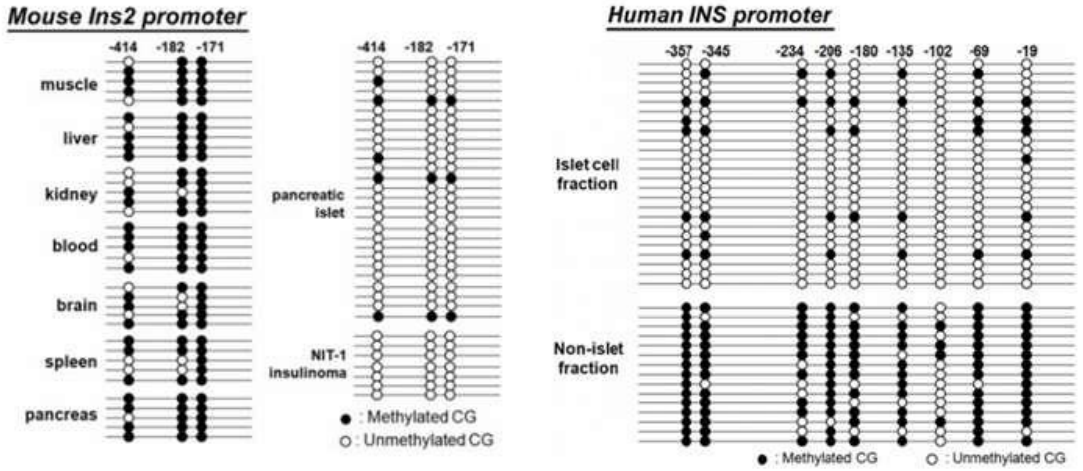
Classic examples of Epigenetics

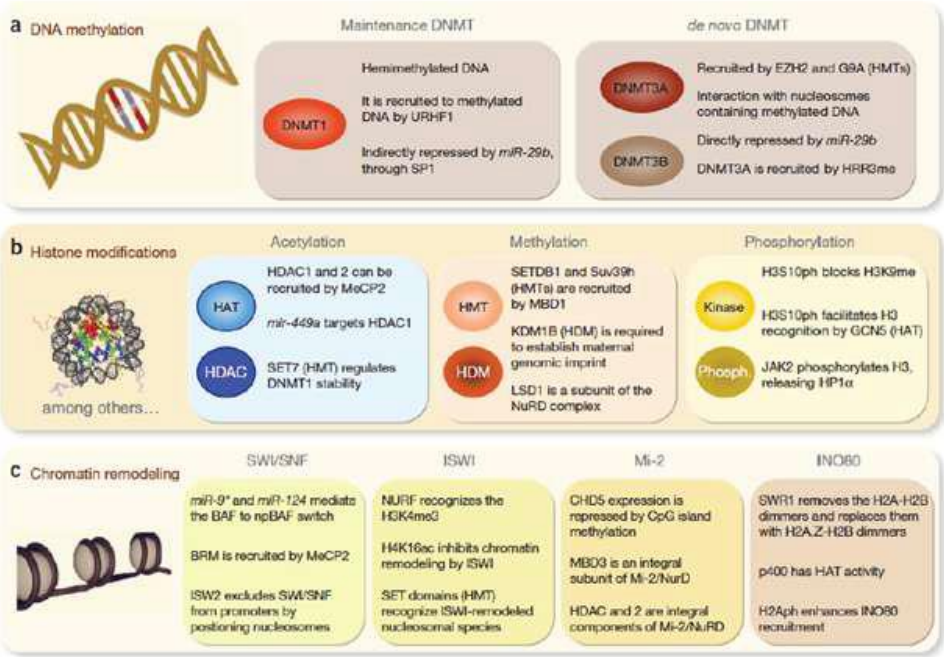




Classic examples of Epigenetics



Epigenetic modifications and human disease
(Portela & Esteller, 2010)
Nat Biotechnol 28:1057-1088

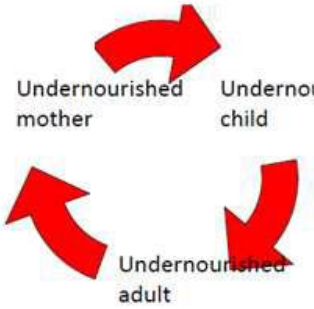


The thrifty genotype hypothesis

Arya M. Sharma

The *thrifty-genotype* hypothesis and its implications for the study of complex genetic disorders in man

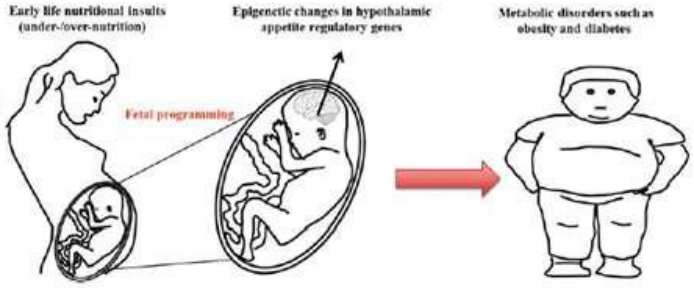
J Mol Med (1998) 76:568–571



Obese adult

Epidemiological transition

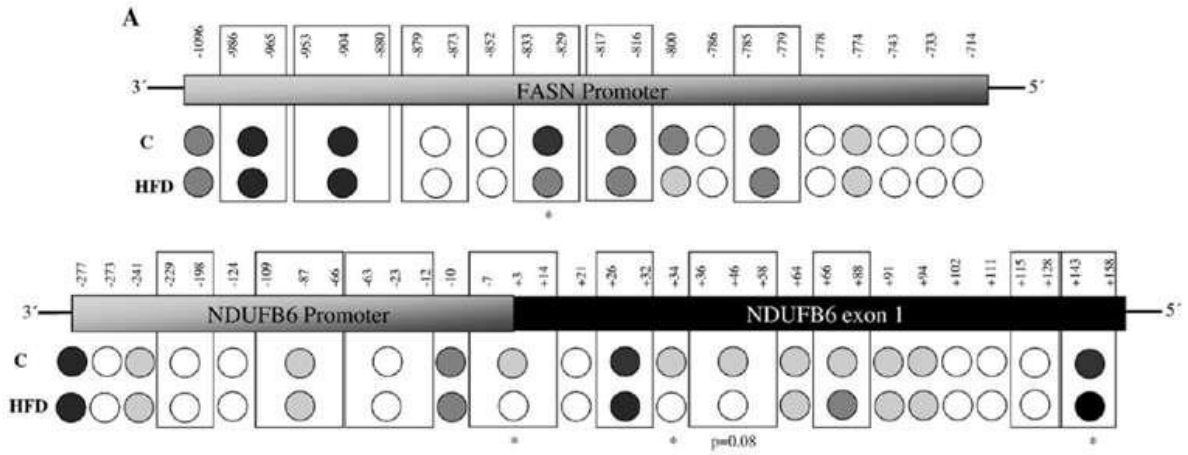
The vicious cycle of undernutrition



Weight gain induced by an isocaloric pair-fed high fat diet: a nutriepigenetic study on FASN and NDUFB6 gene promoters

(Lomba et al, 2010)

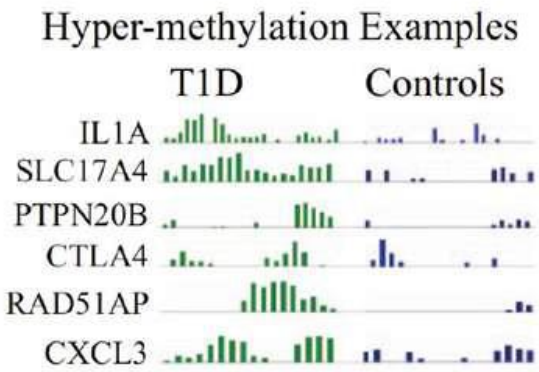
Mol Genet Metab 101:273-278.

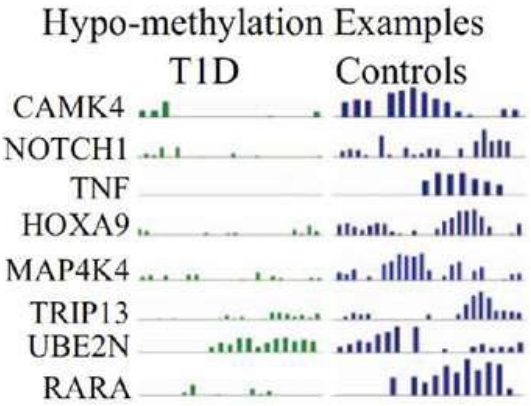


Lymphocytes from patients with type 1 diabetes display a distinct profile of chromatin histone H3 lysine 9 dimethylation: an epigenetic study in diabetes

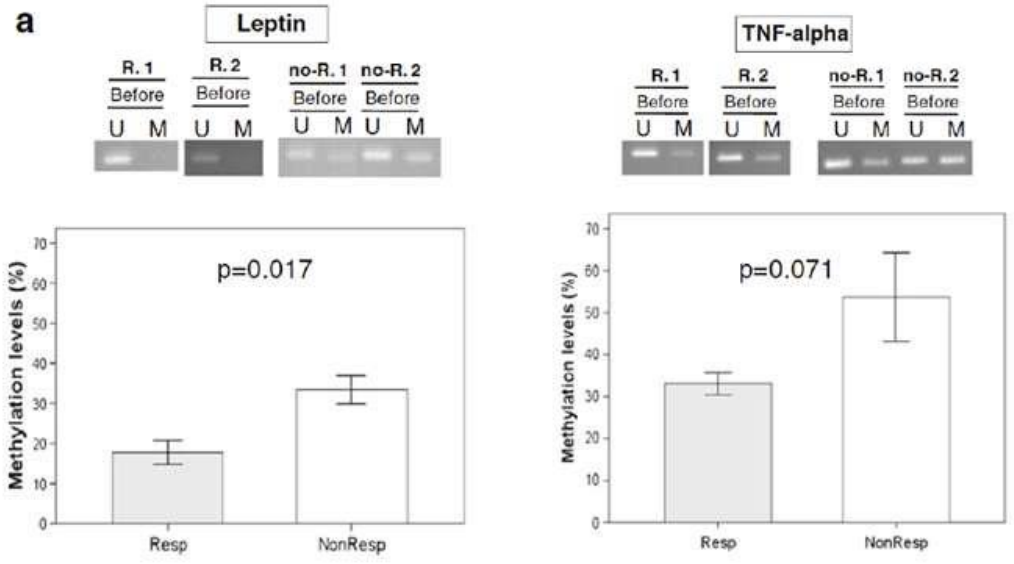
(Miao et al, 2008)

Diabetes 57:3189-3198.



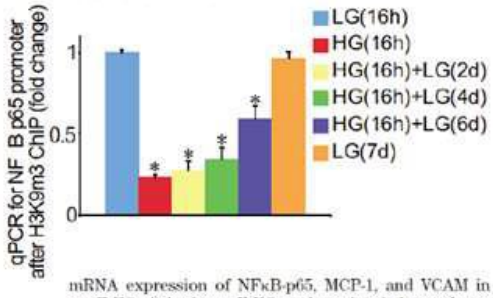


Leptin and TNF-alpha promoter methylation levels measured by MSP could predict the response to a low-calorie diet.
(Cordero et al, 2011)
J Physiol Biochem 67:463-470



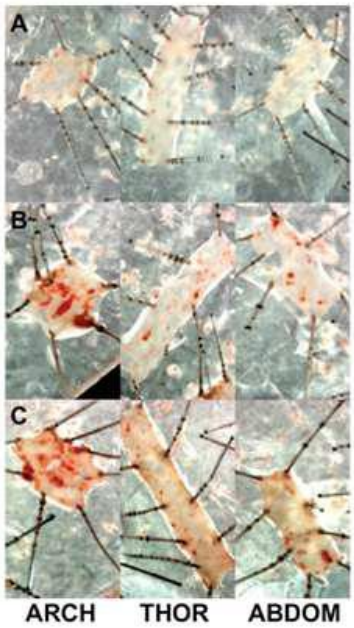
Hyperglycemia induces a dynamic cooperativity of histone methylase and demethylase enzymes associated with gene-activating epigenetic marks that coexist on the lysine tail

(Brasacchio et al, 2009)
Diabetes 58:1229-1236



mRNA expression of NFκB-p65, MCP-1, and VCAM in control apoE KO, diabetic apoE KO, and previously hyperglycemic apoE KO mice

	n	NFκB-p65	MCP-1	VCAM-1
Control apoE KO (NG→NG)	5	1.0 ± 0.2	1.1 ± 0.2	1.0 ± 0.2
Diabetic apoE KO (HG→HG)	5	2.5 ± 0.9*	3.2 ± 1.1*	3.2 ± 0.5*
Previously hyperglycemic apoE KO (HG→NG)	4	2.7 ± 1.1*	3.7 ± 0.9*	1.9 ± 0.06*†



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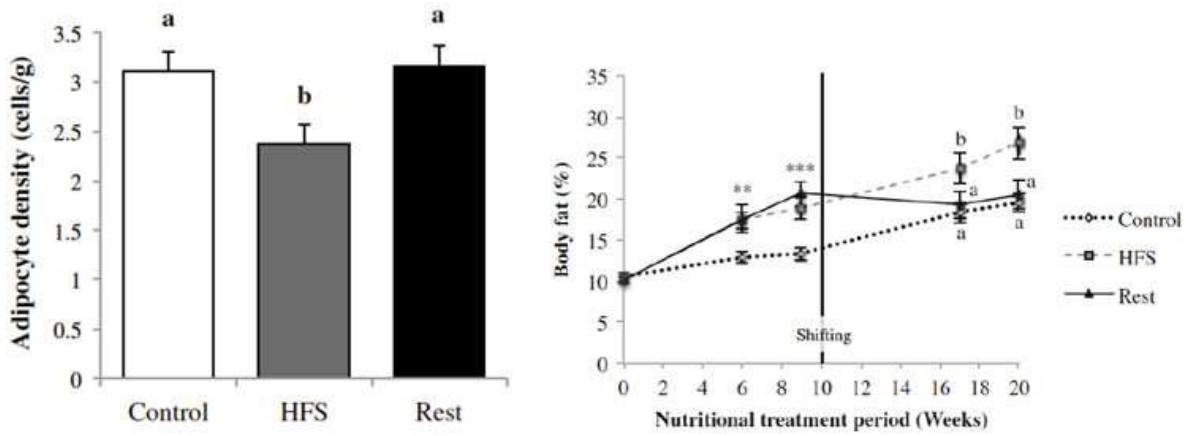
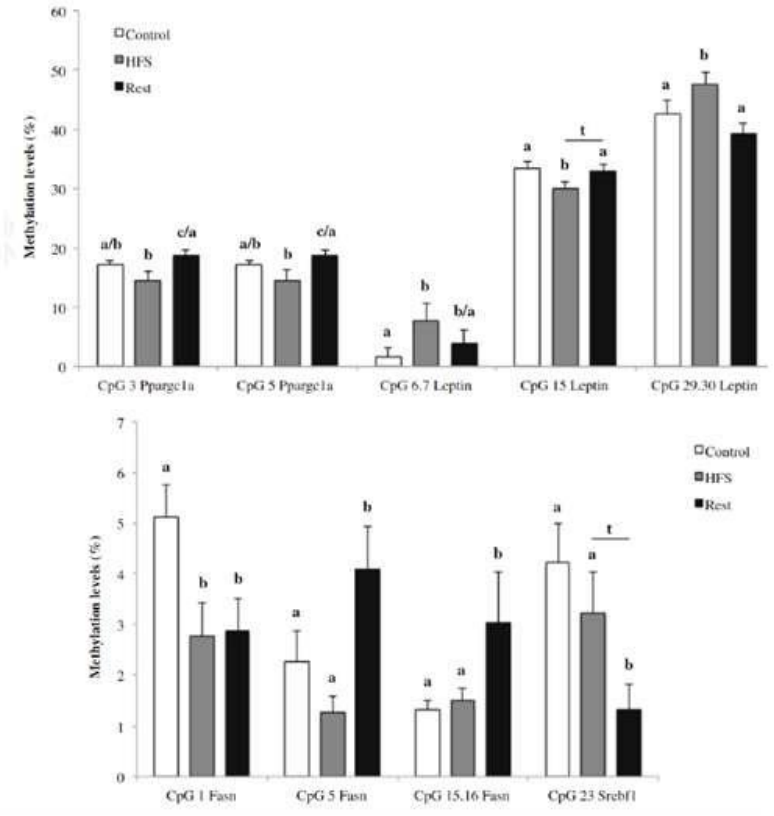
Shifting to a control diet after a high-fat, high-sucrose diet intake induces epigenetic changes in retroperitoneal adipocytes of Wistar rats
(Uriarte et al, 2013)
J Physiol Biochem

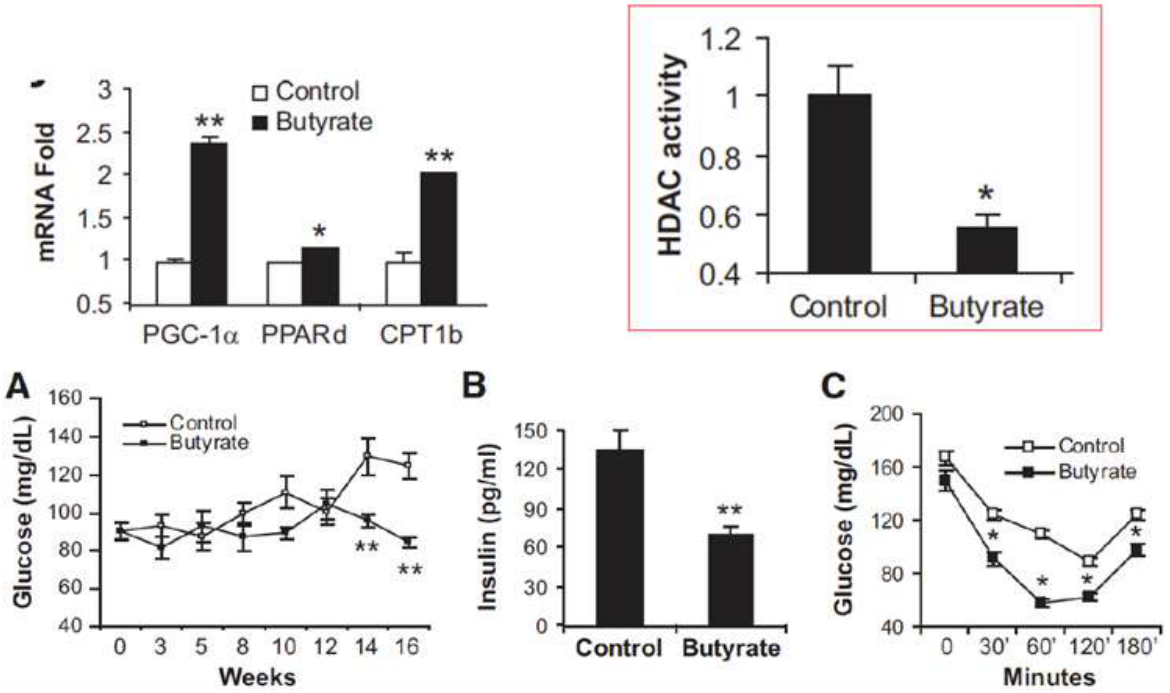



Control
HFS
Rest
Methylation levels (%)
CpG 3 Pparge1a
CpG 5 Pparge1a
CpG 6.7 Leptin
CpG 15 Leptin
CpG 29.30 Leptin
CpG 1 Fasn
CpG 5 Fasn
CpG 15.16 Fasn
CpG 23 Srebf1

Butyrate Improves Insulin Sensitivity and Increases Energy Expenditure in Mice

(Gao et al, 2009)

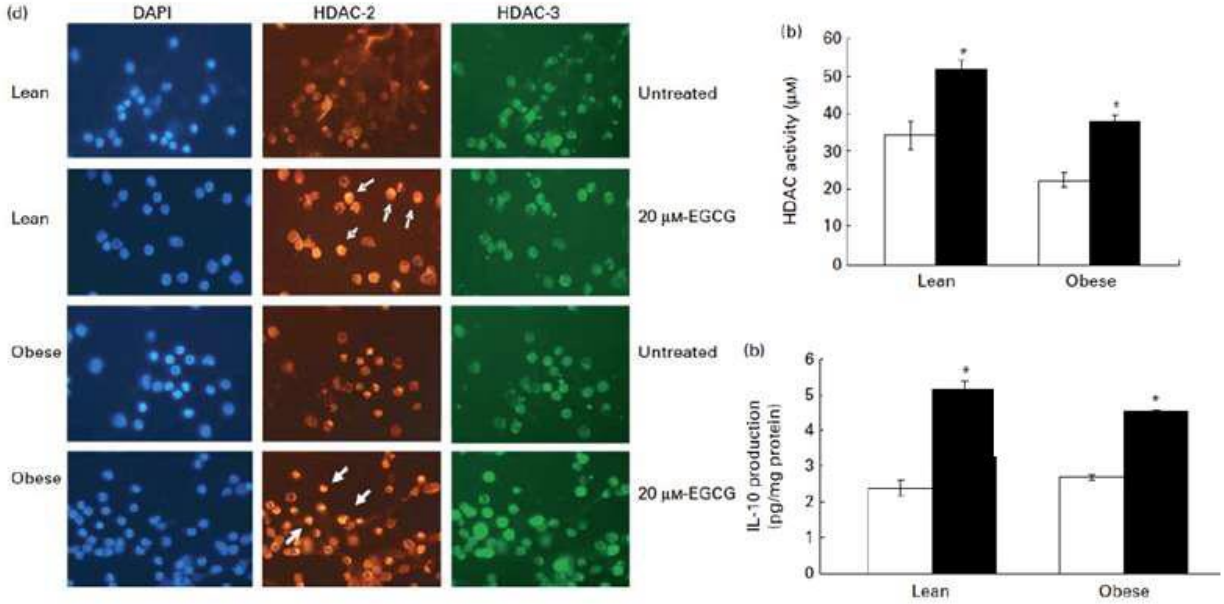
Diabetes 58:1509-1517.



Effects of epigallocatechin gallate on regulatory T cell number and function in obese v lean volunteers

(Yun et al, 2010)

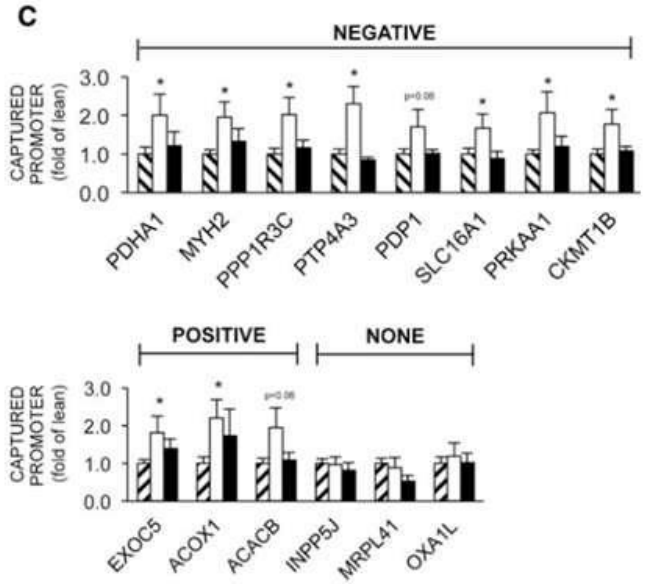
Br J Nutr 103:1771-1777

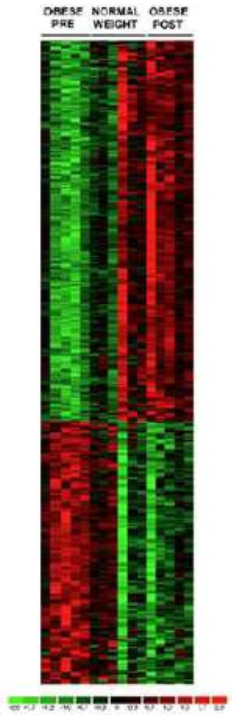


Weight loss after gastric bypass surgery in human obesity remodels promoter methylation.

(Barres et al, 2013)

Cell Rep, 3:1020-1027

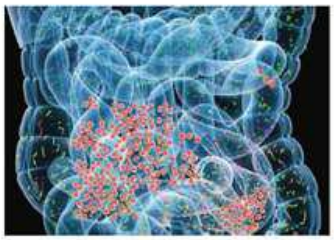




Conclusions

1. There is some evidence that various genetic polymorphisms might influence the development of metabolic symbol.
2. Lifestyle interventions could reduce the risk of developing insulin resistance in individuals with genetic risk.
3. There is evidence that some nutritional treatments based on genetic information have been successful.
4. It is highly recommended that personalized treatments rely on nutritional recommendations based on evidence.
5. Epigenetic modifications play an important role in the development of insulin resistance. Fortunately, many of them are reversible.

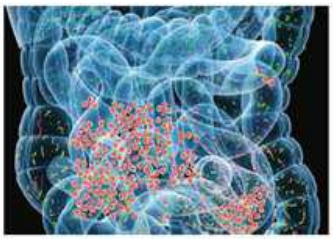
INTRODUCTION TO THE HUMAN MICROBIOTA



1. **Introduction**
   - What is metagenomics?
   - Metagenome sequencing methods
   - Terms: microbiota and microbiome

2. **The Human Microbiota**
   - Microbial composition
   - Gut Microbiota: el gran órgano olvidado
   - Interindividual variability : microbial footprint
   - Main bacteria phyla. Enterotype classification.
   - Development and stability of the microbiota
   - Main factors modulating the microbiota
   - Implication in human physiology
   - Main study models

INTRODUCTION TO THE HUMAN MICROBIOTA



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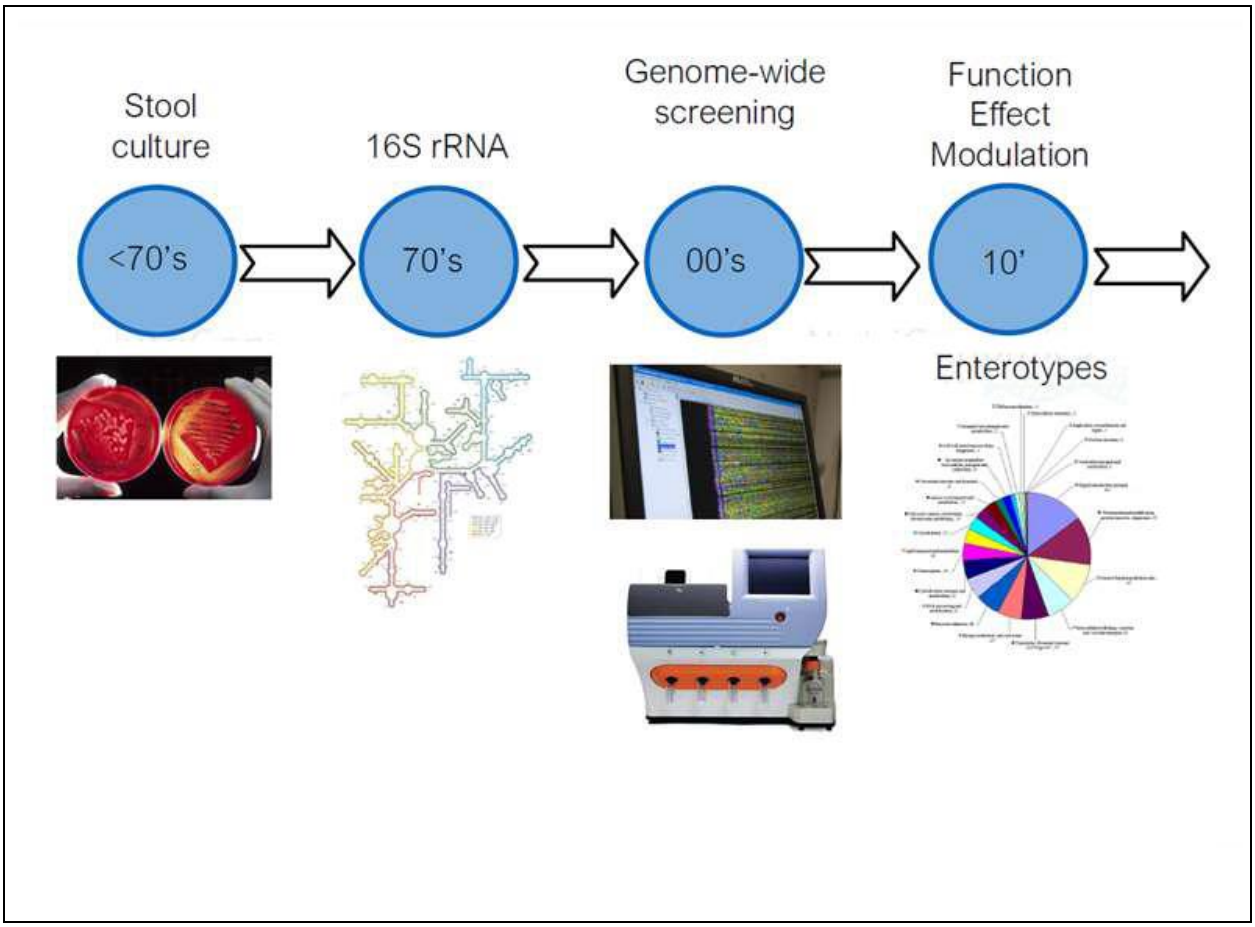
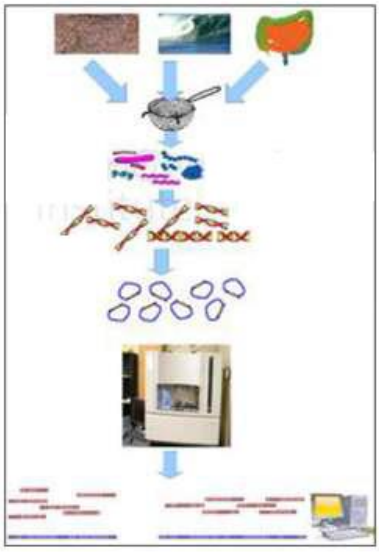

Stool culture
<70's
16S rRNA
70's
Genome-wide screening
00's
Function Effect Modulation
10'
Enterotypes

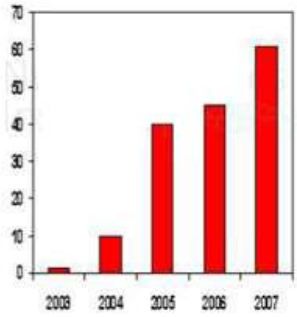
METAGENOMICS: Science that studies all the genetic material of a microbial community without the need to isolate and cultivate microorganisms in a laboratory.



There has been a major boom in recent years:

- Massive sequencing techniques
- Development of biocomputing tools for the analysis of large amounts of information

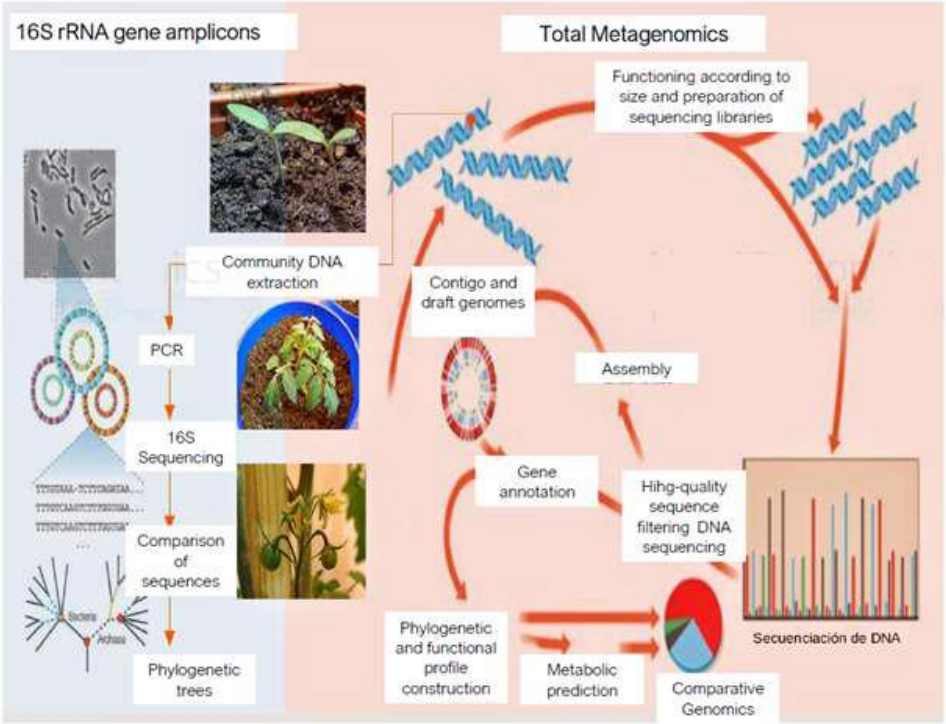
METAGENOMICS: Science that studies all the genetic material of a microbial community without the need to isolate and cultivate microorganisms in a laboratory.



Number of genomes sequenced

There has been a major boom in recent years:

- Massive sequencing techniques
- Development of biocomputing tools for the analysis of large amounts of information


16S rRNA gene amplicons
Total Metagenomics
Functioning according to size and preparation of sequencing libraries
Community DNA extraction
Contigo and draft genomes
PCR
Assembly
16S Sequencing
Gene annotation
Hihg-quality sequence filtering DNA sequencing
Comparison of sequences
Phylogenetic and functional profile construction
Metabolic prediction
Secuenciación de DNA
Phylogenetic trees
Comparative Genomics

TERMS: MICROBIOTA AND MICROBIOME

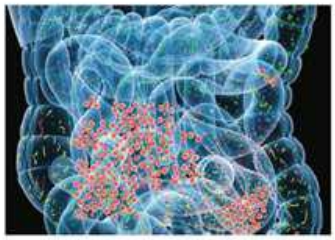
Microbiota

Whole of all the microorganisms that make up a community.

Microbiome

Whole of the genomes and genes of all the microbes that make up a community.

INTRODUCTION TO THE HUMAN MICROBIOTA



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HMP
Meta
HIT

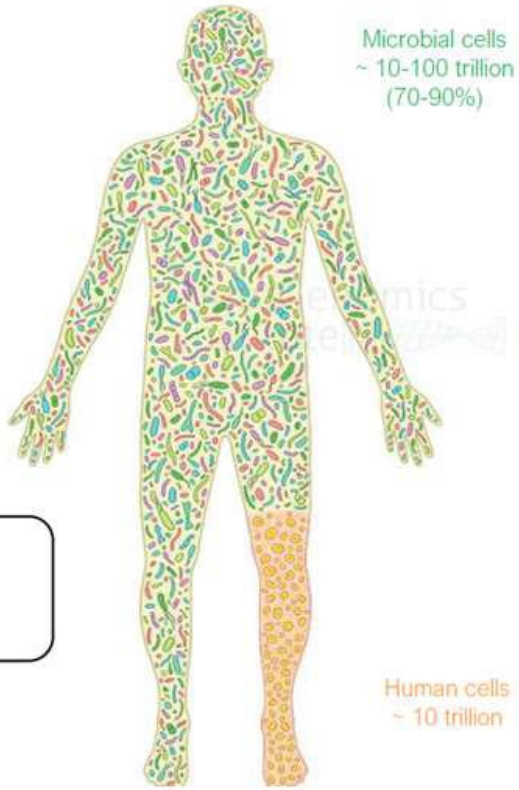
Human Microbiota

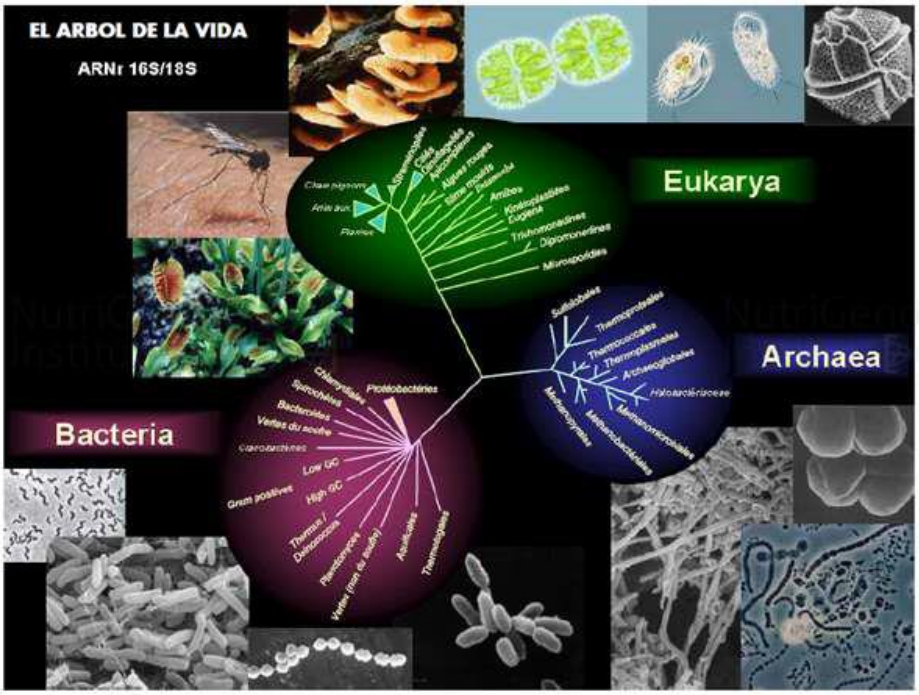
microbes living in our body outnumber cells by ten to one

Human Microbiome

150 times more genes than in the human genome

(99.9% of the human being genetic capacity)

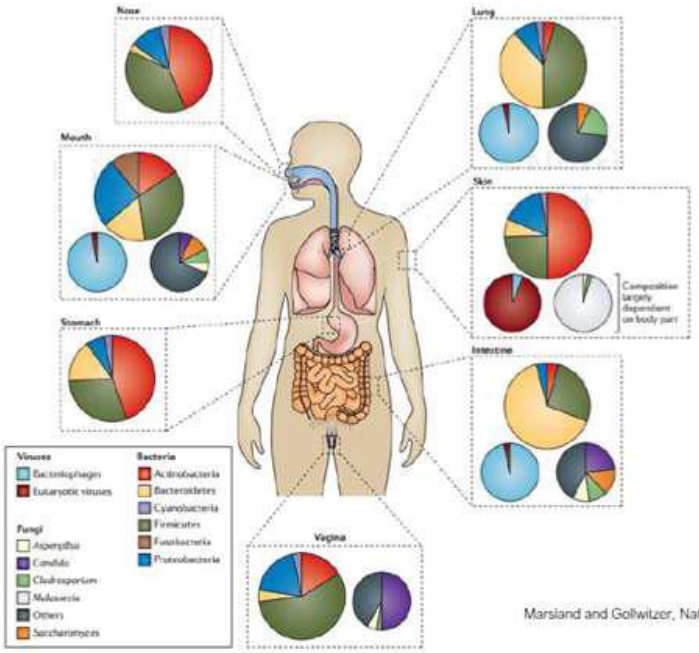




Viruses

Ebola virus

HUMAN MICROBIOTA COMPOSITION IN DIFFERENT PARTS OF THE BODY



Marsland and Gollwitzer, Nature Reviews. 2014, 14:827-835

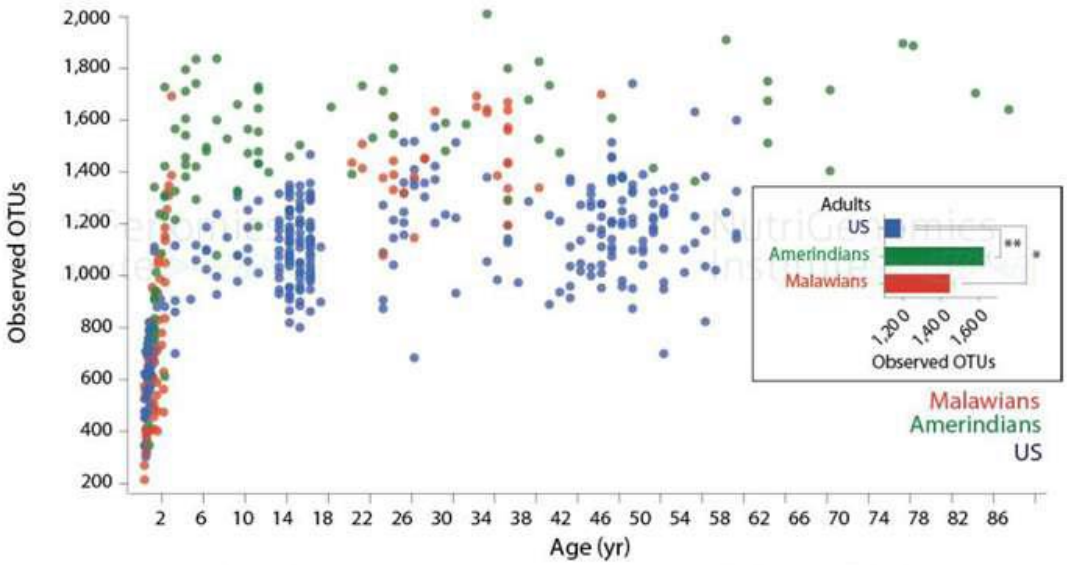
GUT MICROBIOTA: "THE GREAT FORGOTTEN ORGAN"

~ 10^{13}-10^{14} microbes (1-1.5 kg)

> 1000 species

> 7000 strains

HOW DIVERSE IS MICROBIOTA IN AN ADULT?



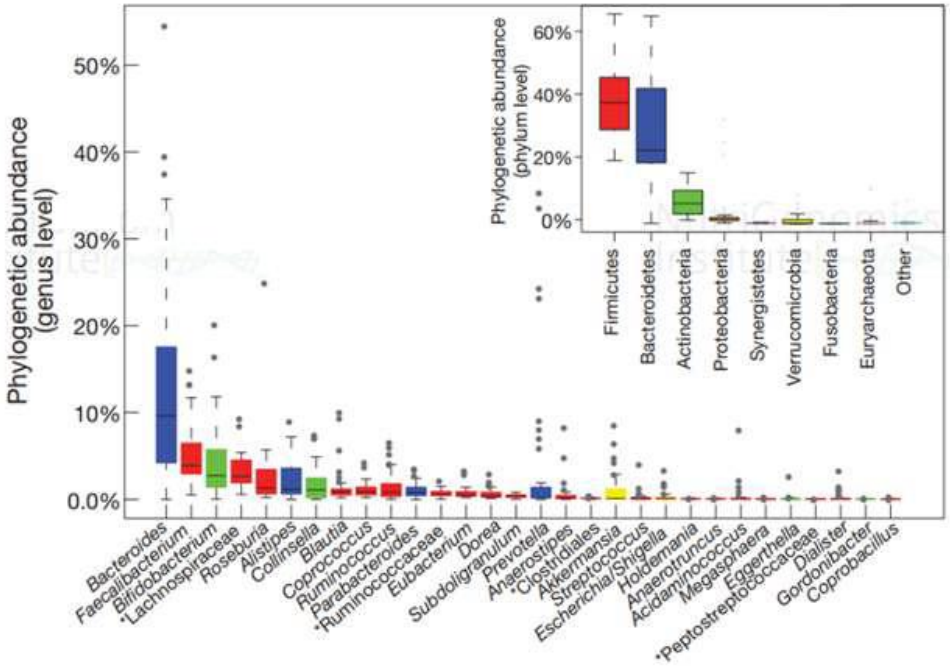
Americans have 15 to 25 percent less microbial diversity than Amerindians and Malawians.
(An OTU is an Operational Taxonomic Unit, a species of bacteria in this context.)

Yatsunenko u et al. Science 2011

EACH INDIVIDUAL'S MICROBIOME IS UNIQUE

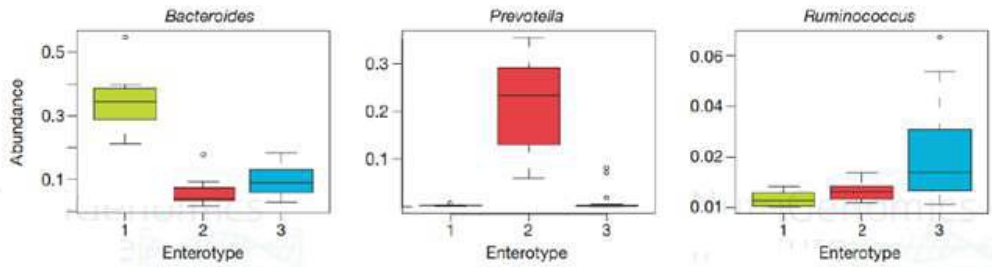
"MICROBIAL FOOTPRINT"

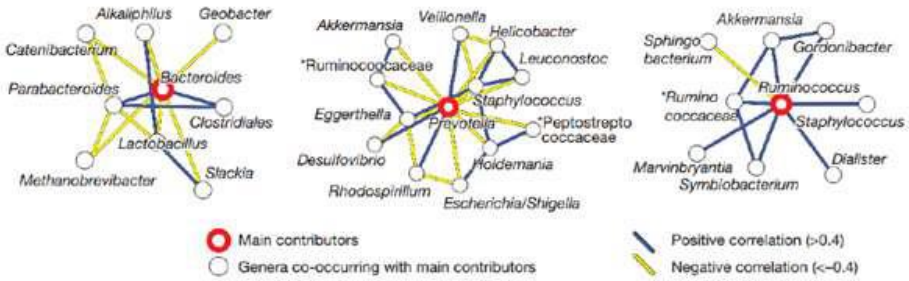
PHYLOGENETIC PROFILE OF HUMAN GUT MICROBIOME



M Arumugam et al. Nature 000, 1–7 (2011) doi:10.1038/nature09944

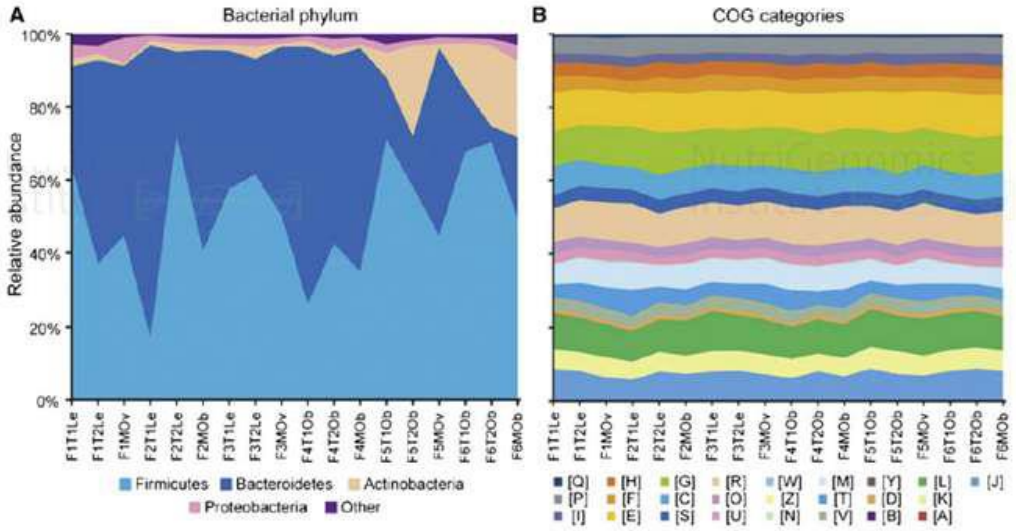
ENTEROTYPES OF THE HUMAN GUT MICROBIOME



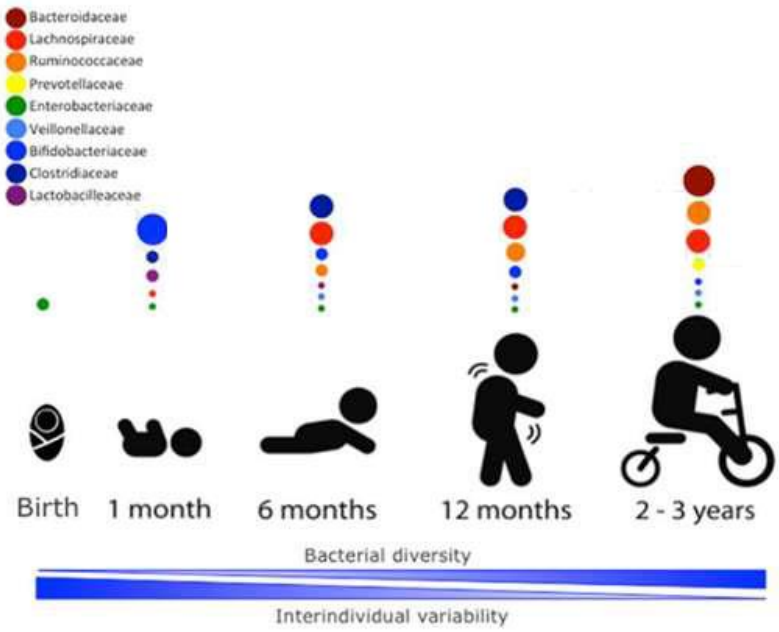


M Arumugam *et al. Nature* 000, 1-7 (2011) doi:10.1038/nature09944

DIFFERENT MICROBIAL COMPOSITIONS CAN PLAY THE SAME ROLE

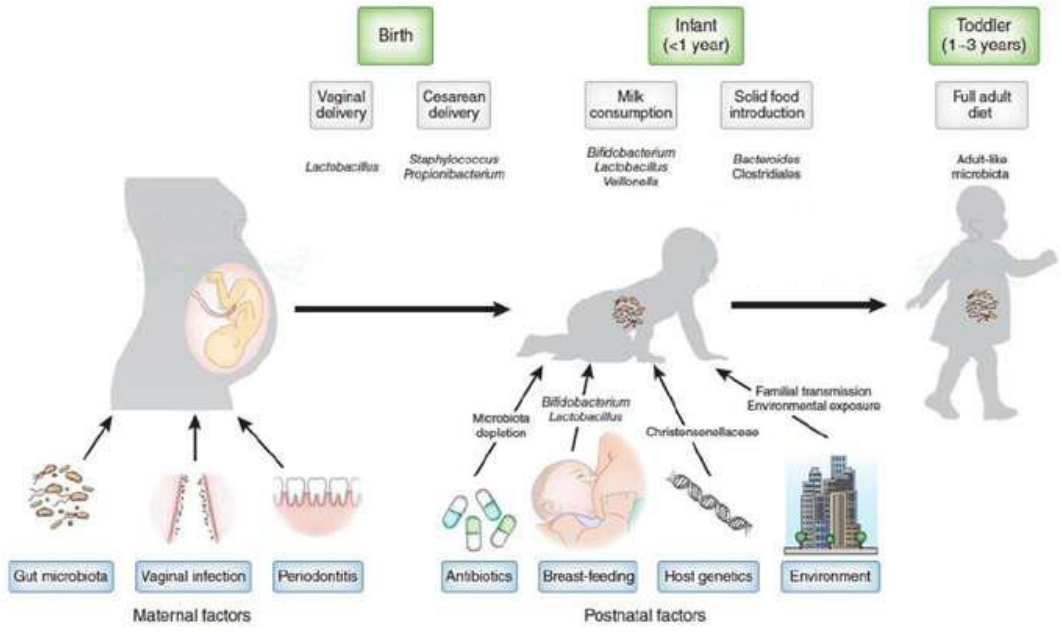


DEVELOPMENT OF THE HUMAN GUT MICROBIOTA

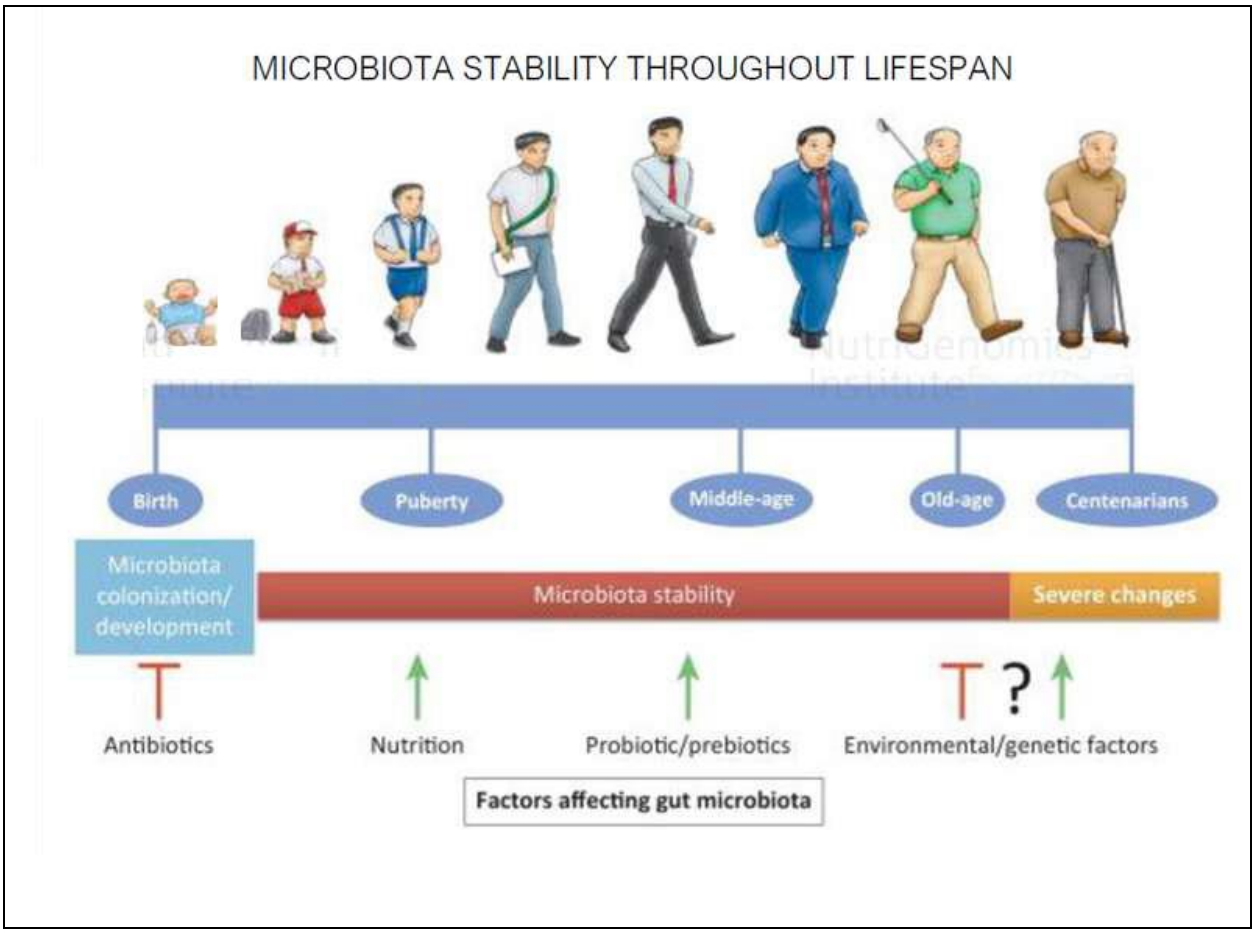


Arrieta *et al.* Frontiers in Immunology. 2014. doi: 10.3389/fimmu.2014.00427

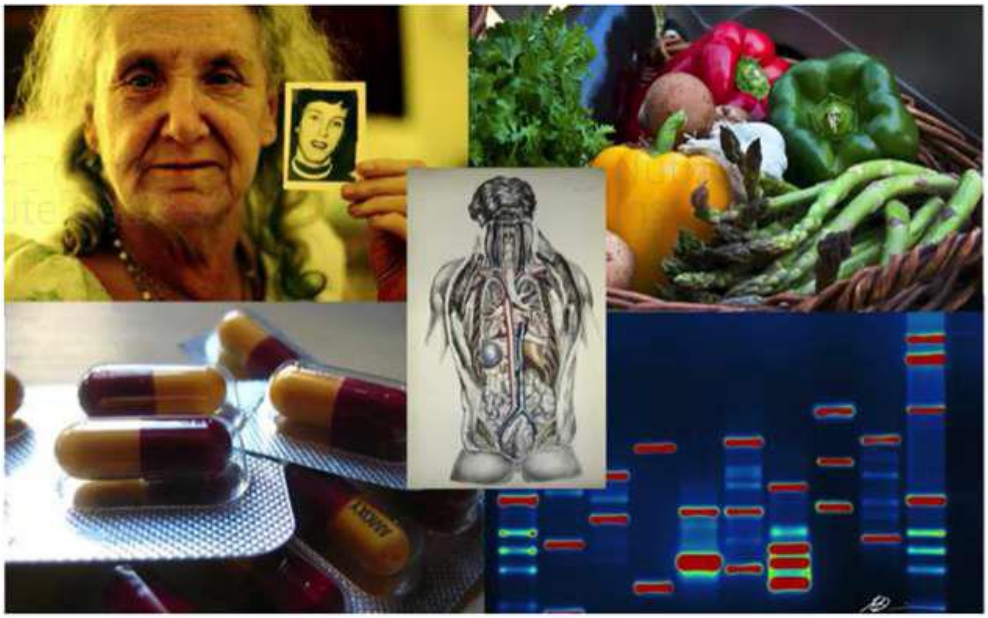
FACTORS AFFECTING THE ESTABLISHMENT OF MICROBIOTA



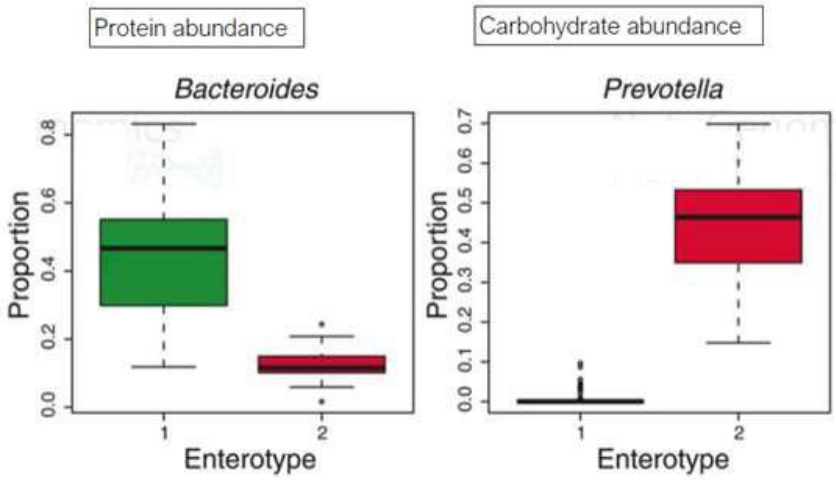
Arrieta et al. Frontiers in Immunology. 2014. doi: 10.3389/fimmu.2014.00427


MICROBIOTA STABILITY THROUGHOUT LIFESPAN
Birth
Puberty
Middle-age
Old-age
Centenarians
Microbiota colonization/ development
Microbiota stability
Severe changes
?
Antibiotics
Nutrition
Probiotic/prebiotics
Environmental/genetic factors
Factors affecting gut microbiota

MAIN FACTORS AFFECTING THE STABILITY OF GUT MICROBIOTA

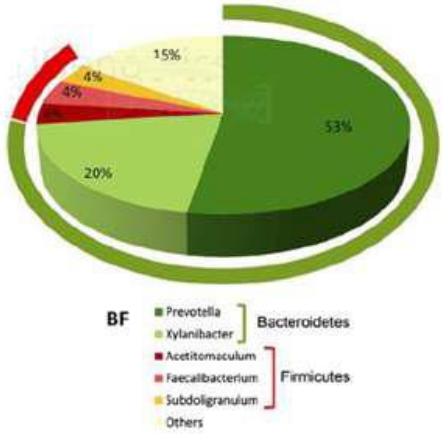


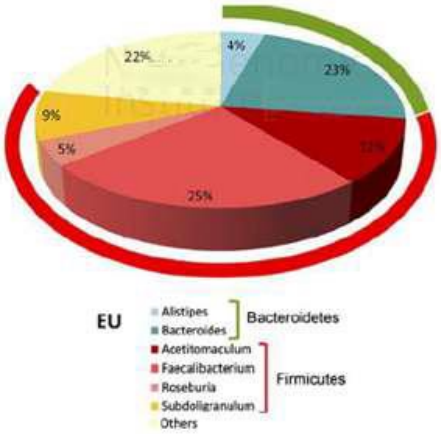
THE DIET AS THE MAIN GUT MICROBIOTA MODULATION FACTOR



Wu et al. Science 2011

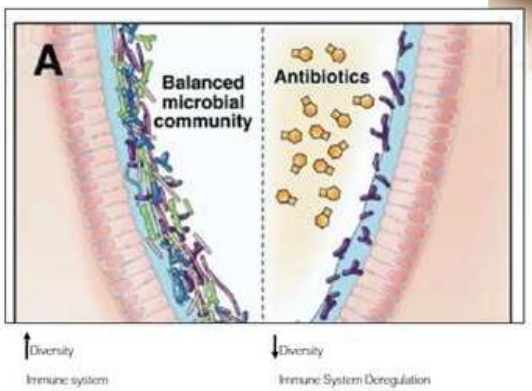
A SPECIFIC DIET DETERMINES A SPECIFIC TYPE OF MICROBES





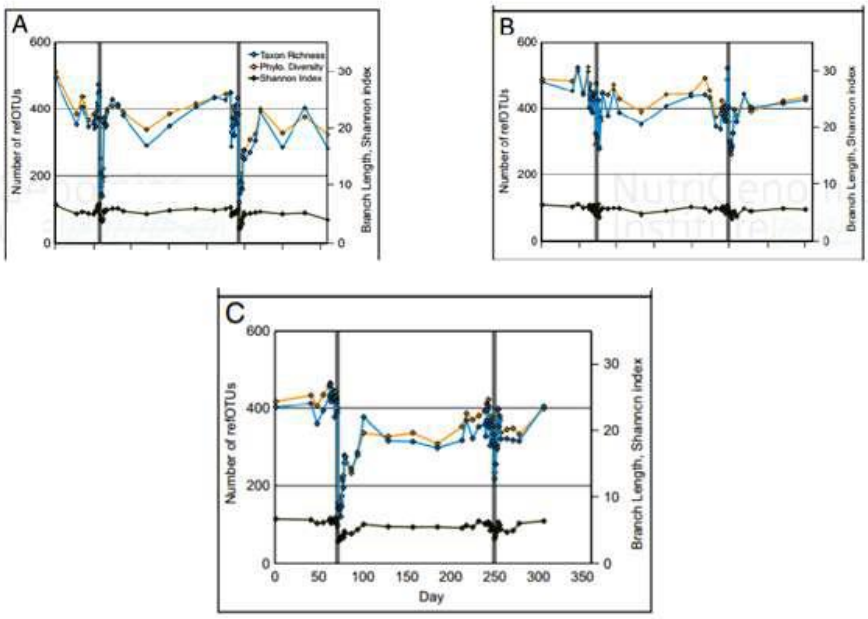
De Filippo et al. PNAS 2010, 17 (33):14691-14696

ANTIBIOTICS CAN MODULATE GUT MICROBIOTA BUT THEY DO SO IN A SELECTIVE MANNER!!!

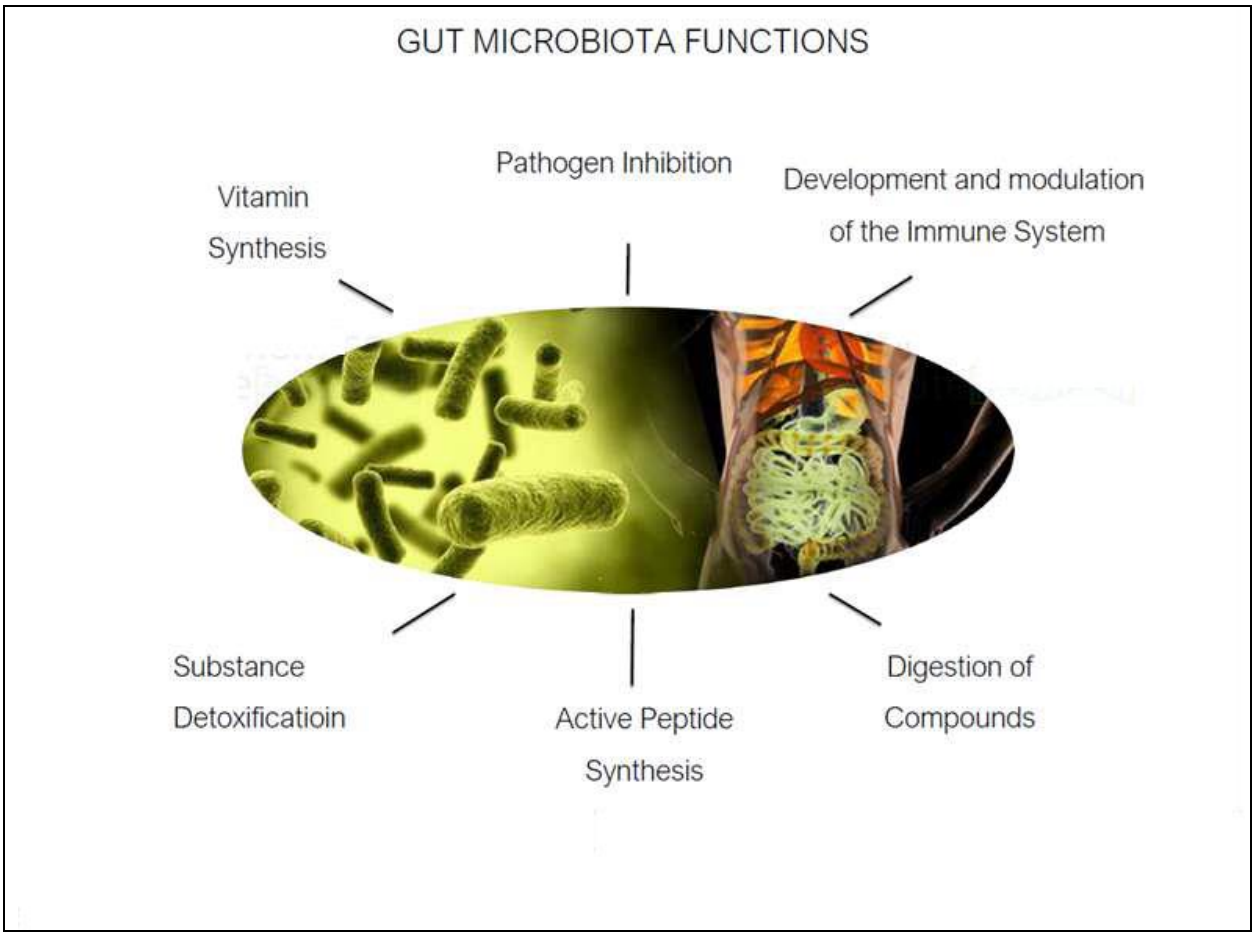


Preidis and Versalovic. Gastroenterology 2009, 136(6):2015-2031

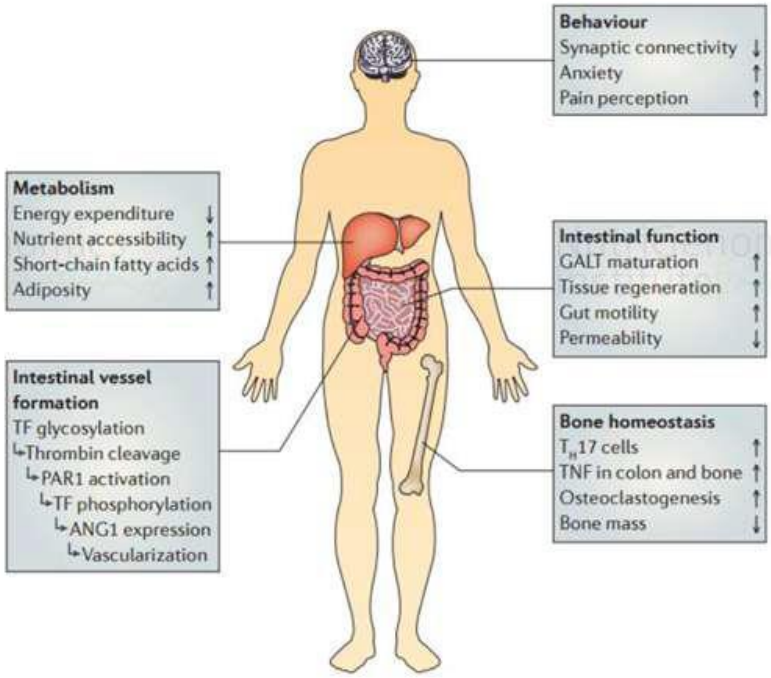
THE EFFECT OF AN ANTIBIOTIC DEPENDS ON THE INDIVIDUAL



Dethlefsen and Relman. PNAS 2011, 108(1):4554-4561

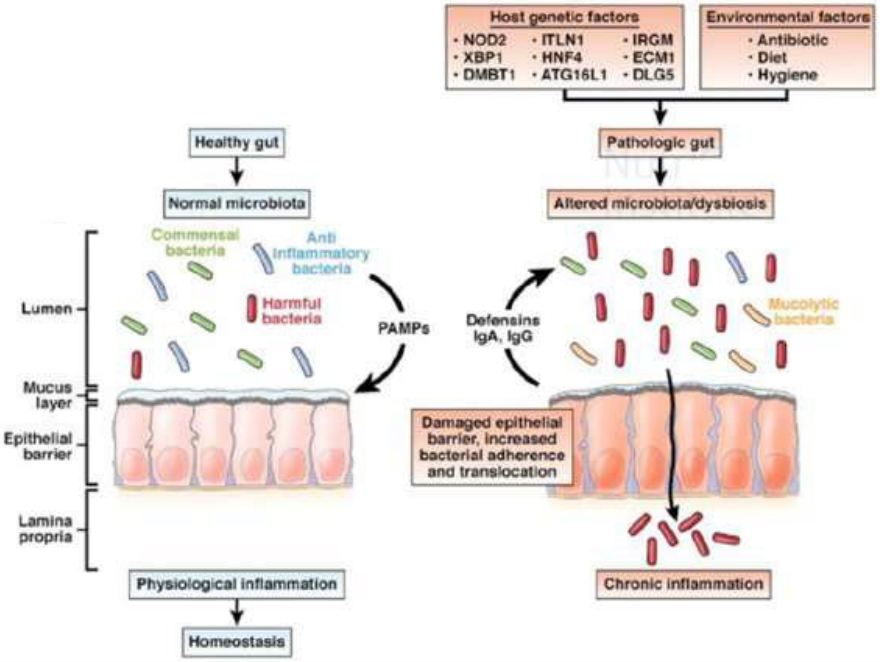

GUT MICROBIOTA FUNCTIONS
Vitamin Synthesis
Pathogen Inhibition
Development and modulation of the Immune System
Substance Detoxificatioin
Active Peptide Synthesis
Digestion of Compounds

MICROBIOTA MODULATES THE HOST PHYSIOLOGY

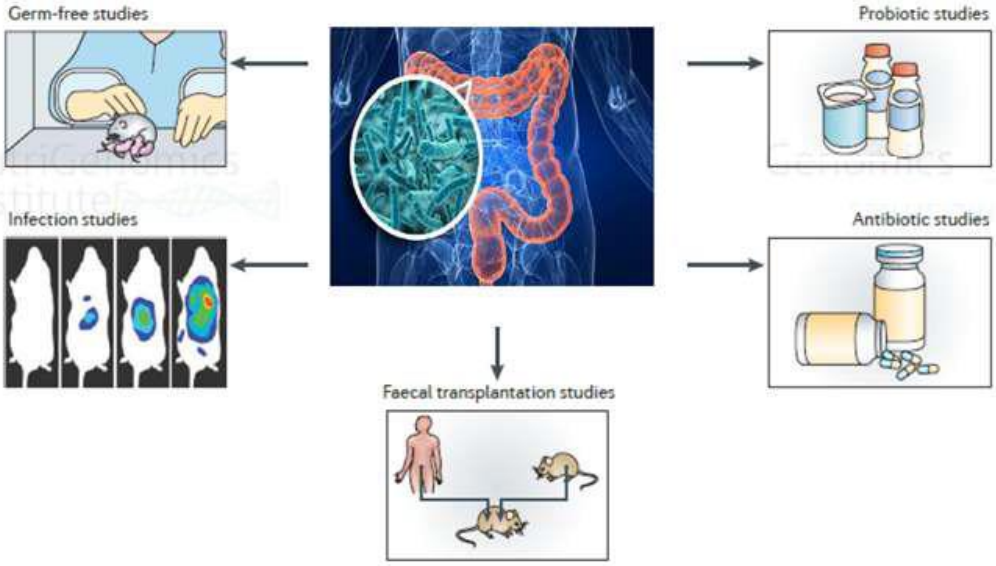


Sommer and Bäckhed. Nature Reviews, 2013. doi:10.1038/nrmicro2974

GUT MICROBIOTA HOMEOSTASIS, KEY TO MAINTAIN A HEALTHY PHYSIOLOGICAL STATE



STUDY MODELS ON THE INFLUENCE OF THE GUT MICROBIOTA ON THE HOST PHYSIOLOGY



Adaptado de Cryan and Dian, Nature Reviews 2012, 13:701-712

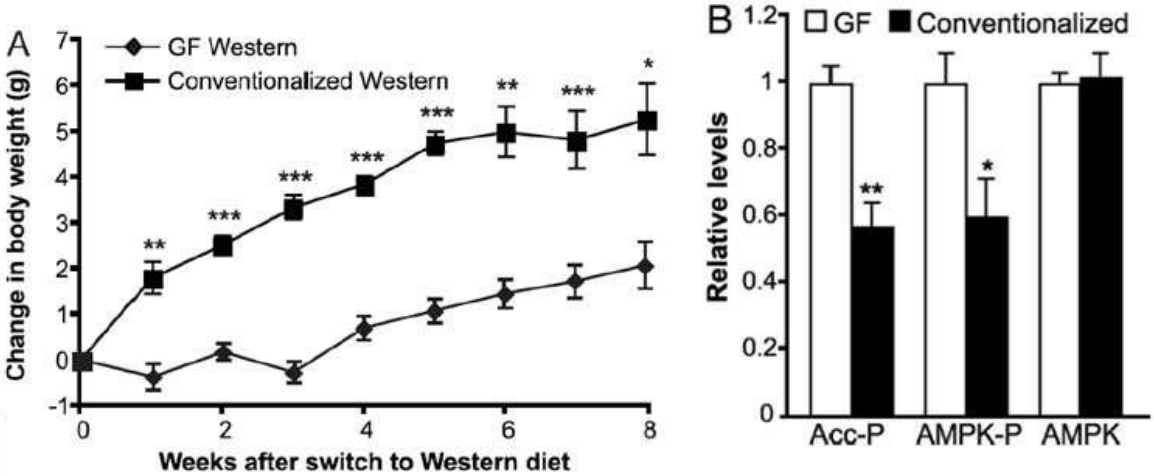
CONCLUSIONS AND COMMENTS

1. The human microbiota is made up of bacteria, fungi, archaea and viruses.
2. The human microbiome is approximately 150 times the human genome.
3. The establishment of the gut microbiota starts during birth and takes place over the first three years of life.
4. The composition of microbiota is unique in each individual, although they can play similar roles.
5. The composition of microbiota can be classified in three enterotypes according to the abundance of three genera of bacteria: bacteroides, prevotella and ruminococcus.
6. Microbiota plays an important role in the host physiology
7. The composition of microbiota can be altered by different factors: exposure to antibiotics, diet, age and host physiology (genetic background).

Microbiota and metabolic syndrome
- Obesity and insulin resistance -

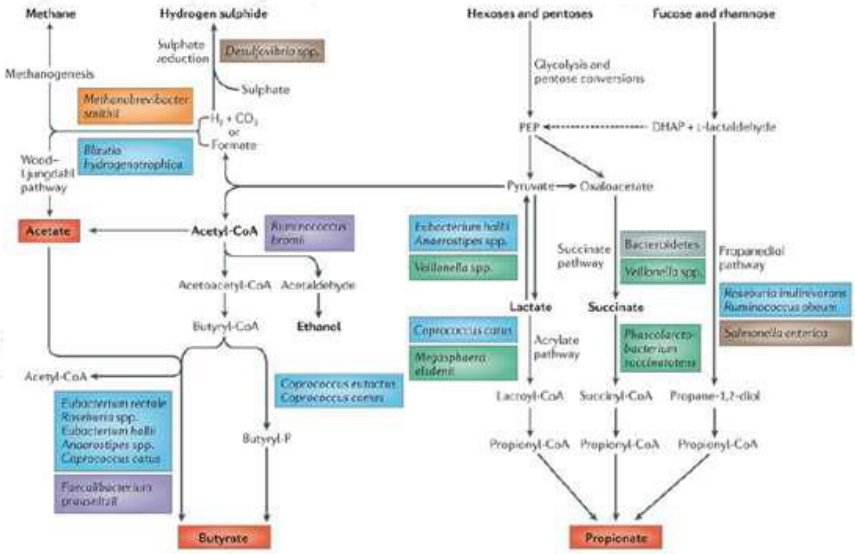
Index

Mechanisms underlying the resistance to diet-induced obesity in germ-free mice
(Backhed et al, 2007)
PNAS 105:2117-2122



Colonic fermentation

Indigestible portion + bacterial flora = Gases (CO_2, H_2, methane)
+ Biomass
+ Short-chain fatty acids (acetic acid, propionic acid, butyric acid)
+ Organic acids (lactic acid, succinic acid, pyretic acid)
+ Other fermentation products (toxic substances, ammonia, amines, nitrosamines), antioxidants, etc.



Microbiota and SCFA in lean and overweight healthy subjects

(Schwiertz et al, 2009)

Obesity 18:190-195.

Table 2 Mean SCFA (mmol/l) concentration and gross energy content (kJ/g) in dry feces of volunteers with different BMI

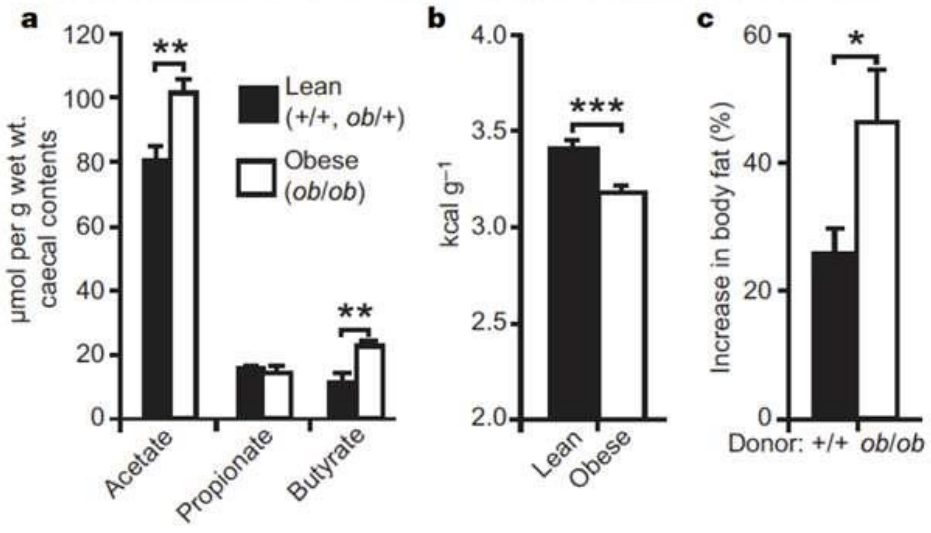
BMI	Category	*n*	Acetate	Propionate	Iso-butyrate	Butyrate	Iso-valerate	Valerate	Total SCFA	Energy
18.5–24.9	Normal	30	50.5 ± 12.6	13.6 ± 5.2	1.8 ± 0.9	14.1 ± 7.6	2.7 ± 2.1	1.9 ± 0.7	84.6 ± 22.9	21.7 ± 1.3
25–30	Overweight	35	56.0 ± 18.2	18.3 ± 7.9[a]	1.6 ± 0.9	18.5 ± 10.1	2.3 ± 1.7	2.0 ± 1.1	98.7 ± 33.9[a]	21.6 ± 1.6
>30	Obesity	33	59.8 ± 18.3	19.3 ± 8.7[a]	1.7 ± 1.2	18.1 ± 10.0	2.8 ± 2.0	2.3 ± 1.1	103.9 ± 34.3[a]	21.6 ± 1.6

[a]Significant increase in comparison to lean volunteers ($P < 0.05$).

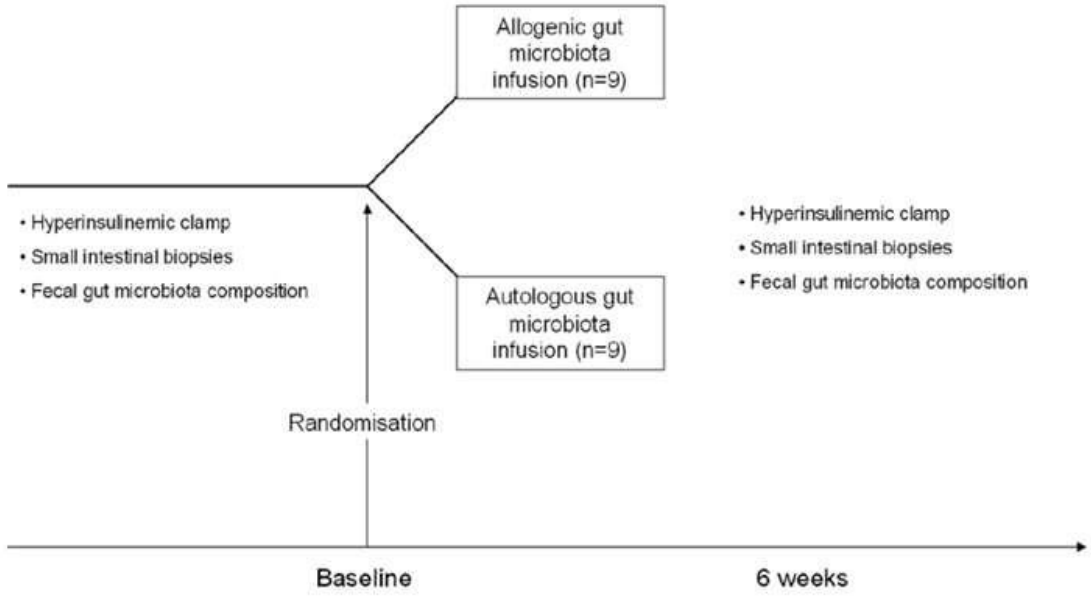
An obesity-associated gut microbiome with increased capacity for energy harvest

(Turnbaugh et al, 2006)

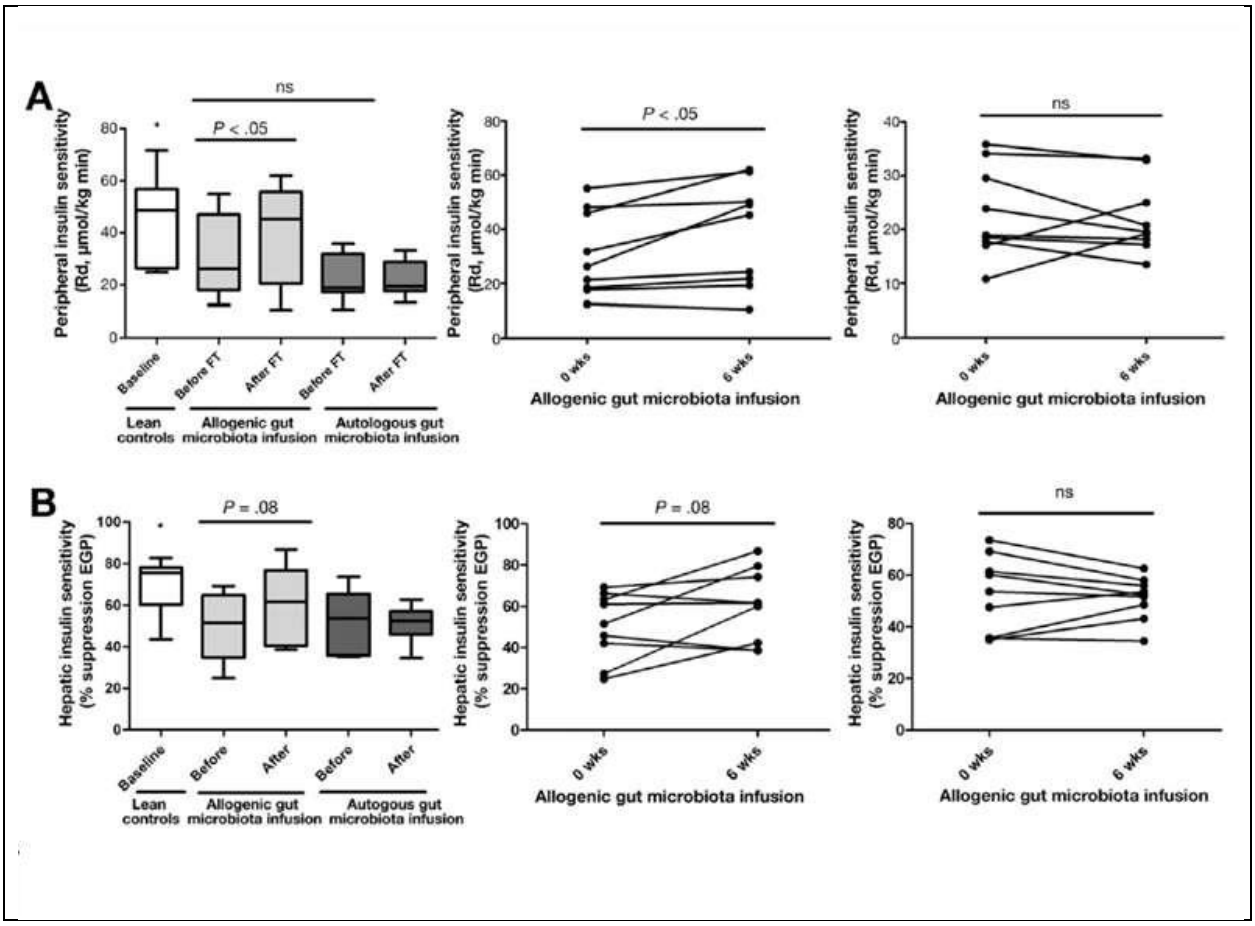
Nature 444:1027-1031



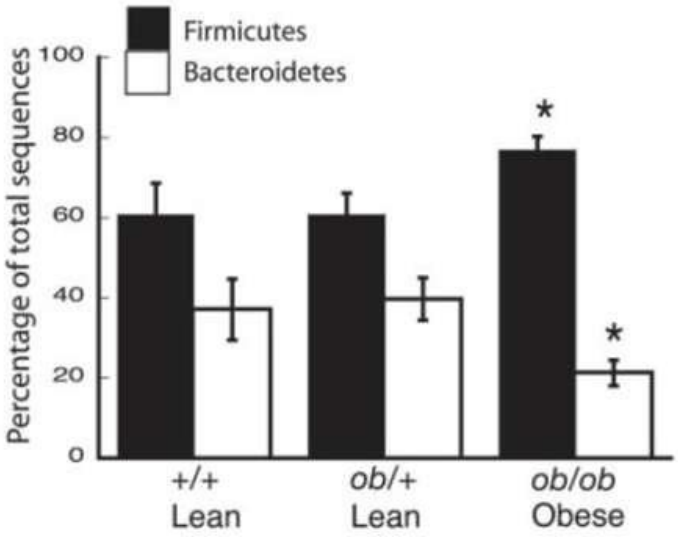
Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome
(Vrieze et al, 2012)
Gastroenterology 143:913



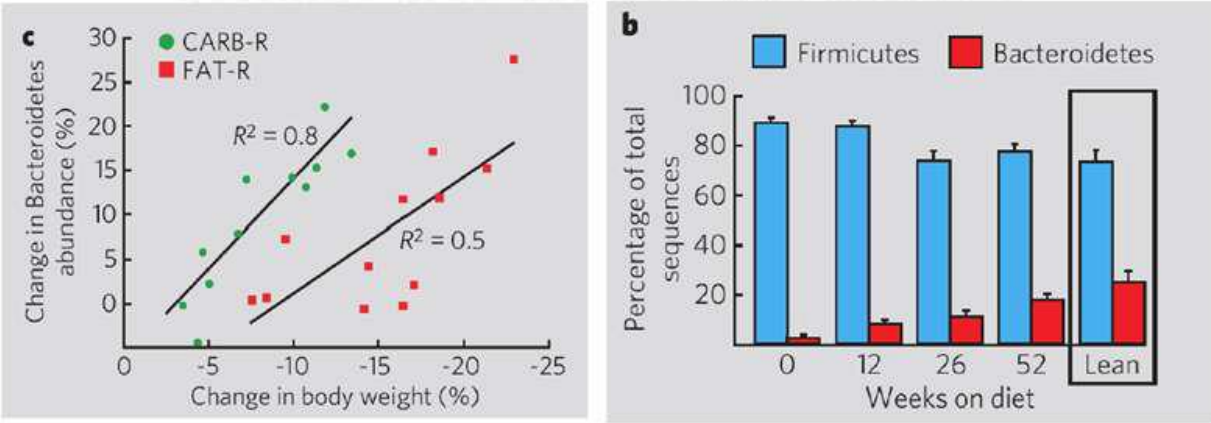
Supplementary Figure 1. Overview of study scheme.


A
ns
P < .05
Peripheral insulin sensitivity (Rd, µmol/kg min)
Baseline
Before FT
After FT
Before FT
After FT
Lean controls
Allogenic gut microbiota infusion
Autologous gut microbiota infusion
P < .05
0 wks
6 wks
Allogenic gut microbiota infusion
ns
0 wks
6 wks
Allogenic gut microbiota infusion
B
P = .08
Hepatic insulin sensitivity (% suppression EGP)
Baseline
Before
After
Before
After
Lean controls
Allogenic gut microbiota infusion
Autogous gut microbiota infusion
P = .08
0 wks
6 wks
Allogenic gut microbiota infusion
ns
0 wks
6 wks
Allogenic gut microbiota infusion

Obesity alters gut microbial ecology.
(Ley et al, 2005)
Proc Natl Acad Sci U S A. 102:11070-5.

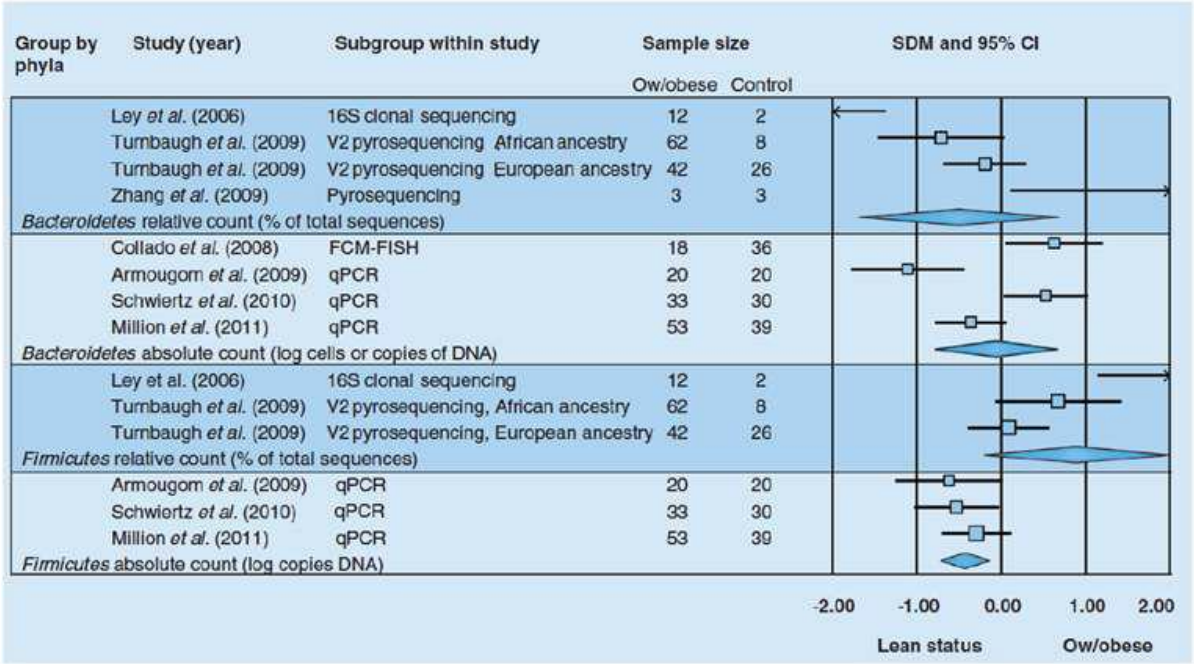


Microbial ecology: Human gut microbes associated with obesity
(Ley et al, 2006)
Nature 444:1022-1023



The relationship between gut microbiota and weight gain in humans

(Angelakis et al, 2012)
Fut Microbiol 7:91-109.



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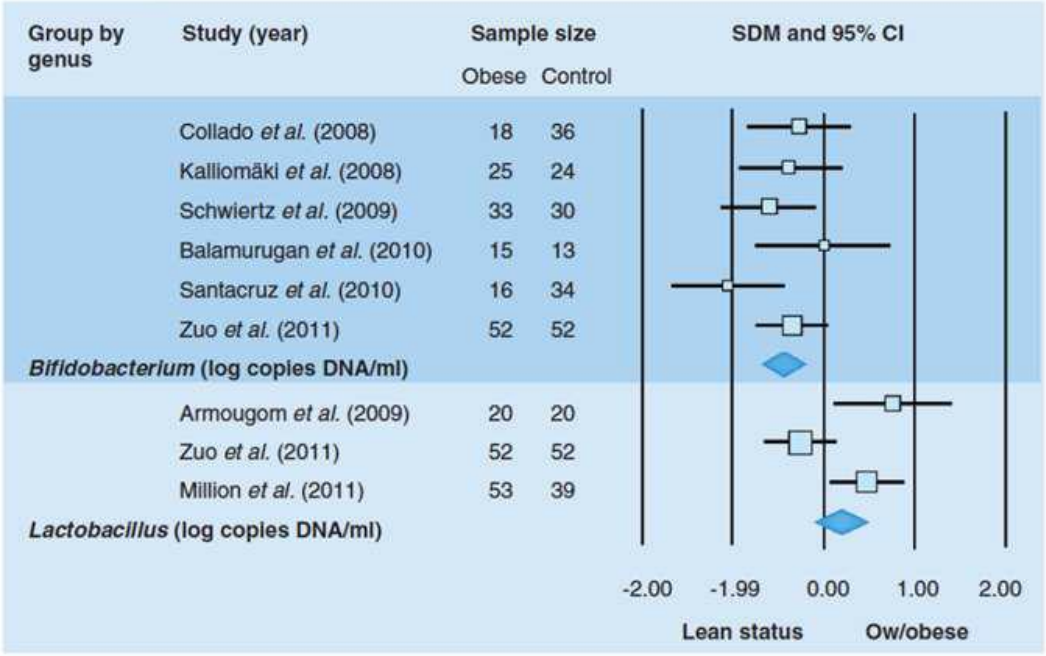
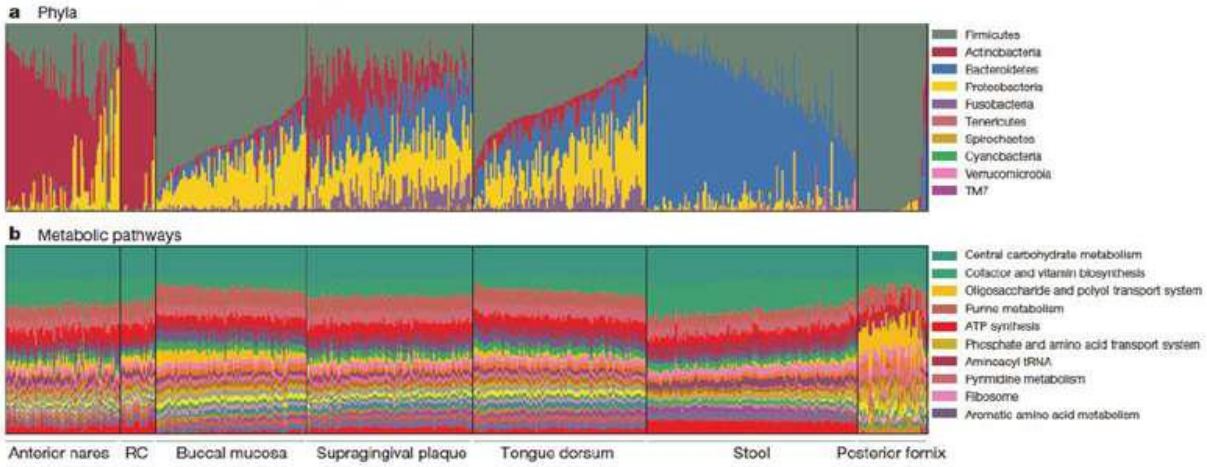


Structure, function and diversity of the healthy human microbiome

The human microbiome project consortium, 2012

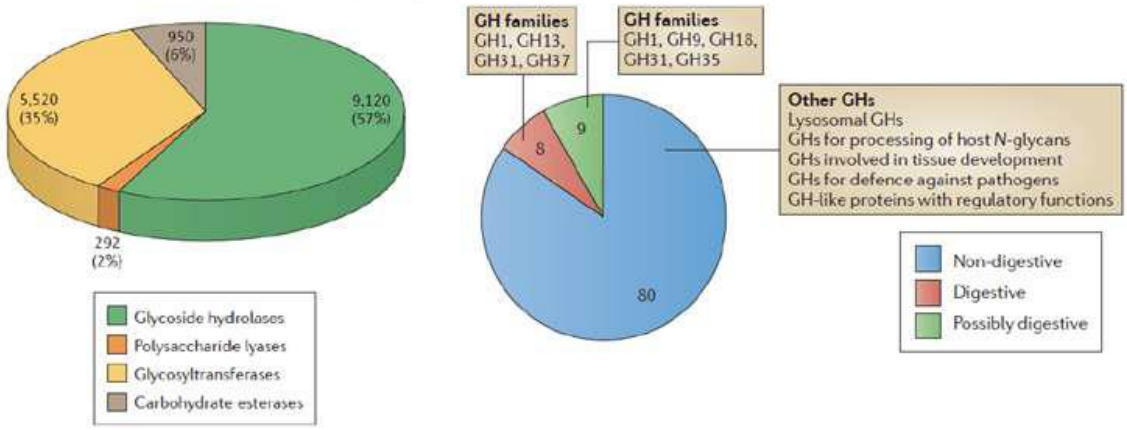
Nature 486, 207-214.

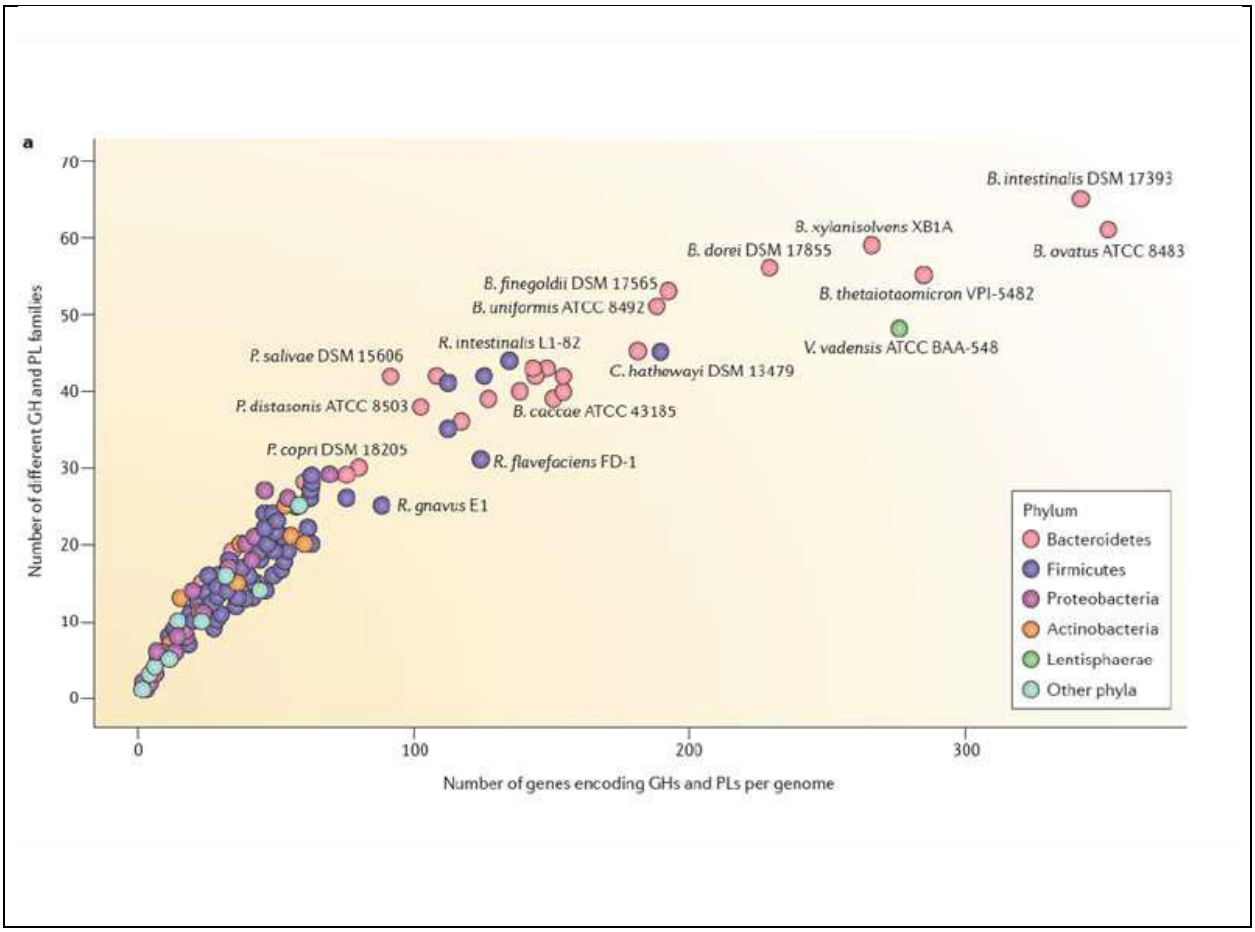


The abundance and variety of carbohydrate-active enzymes in the human gut microbiota

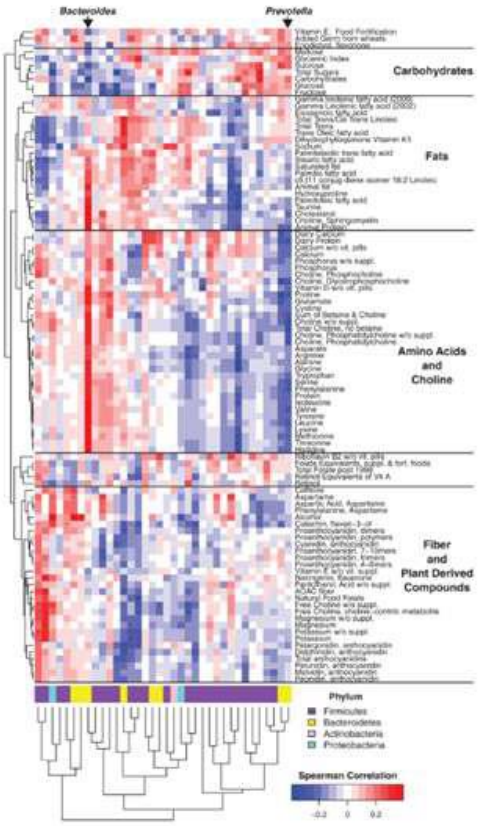
(El Kaoutari et al, 2013)

Nature reviews Microbiology 11:497




a
Number of different GH and PL families
Number of genes encoding GHs and PLs per genome
0
10
20
30
40
50
60
70
0
100
200
300
B. intestinalis DSM 17393
B. xylanisolvens XB1A
B. ovatus ATCC 8483
B. dorei DSM 17855
B. thetaiotaomicron VPI-5482
B. finegoldii DSM 17565
B. uniformis ATCC 8492
V. vadensis ATCC BAA-548
R. intestinalis L1-82
P. salivae DSM 15606
C. hathewayi DSM 13479
P. distasonis ATCC 8503
B. caccae ATCC 43185
P. copri DSM 18205
R. flavefaciens FD-1
R. gnavus E1
Phylum
Bacteroidetes
Firmicutes
Proteobacteria
Actinobacteria
Lentisphaerae
Other phyla

Linking long-term dietary patterns with gut microbial enterotypes
(Wu et al, 2011)
Science 334:105-8.



Microbiota and metabolic syndrome
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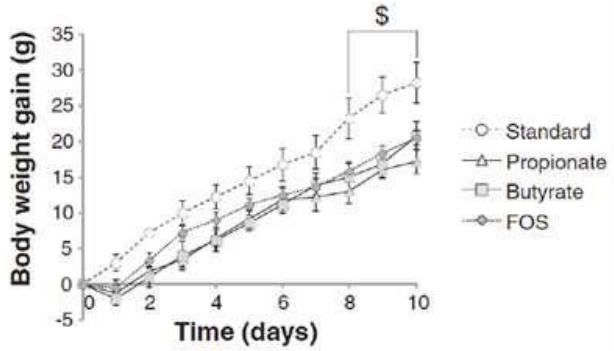
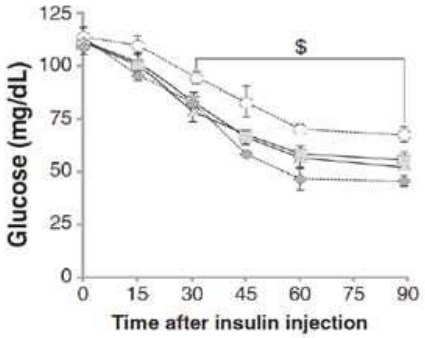
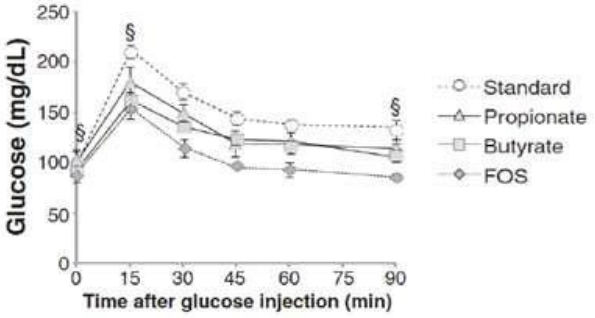
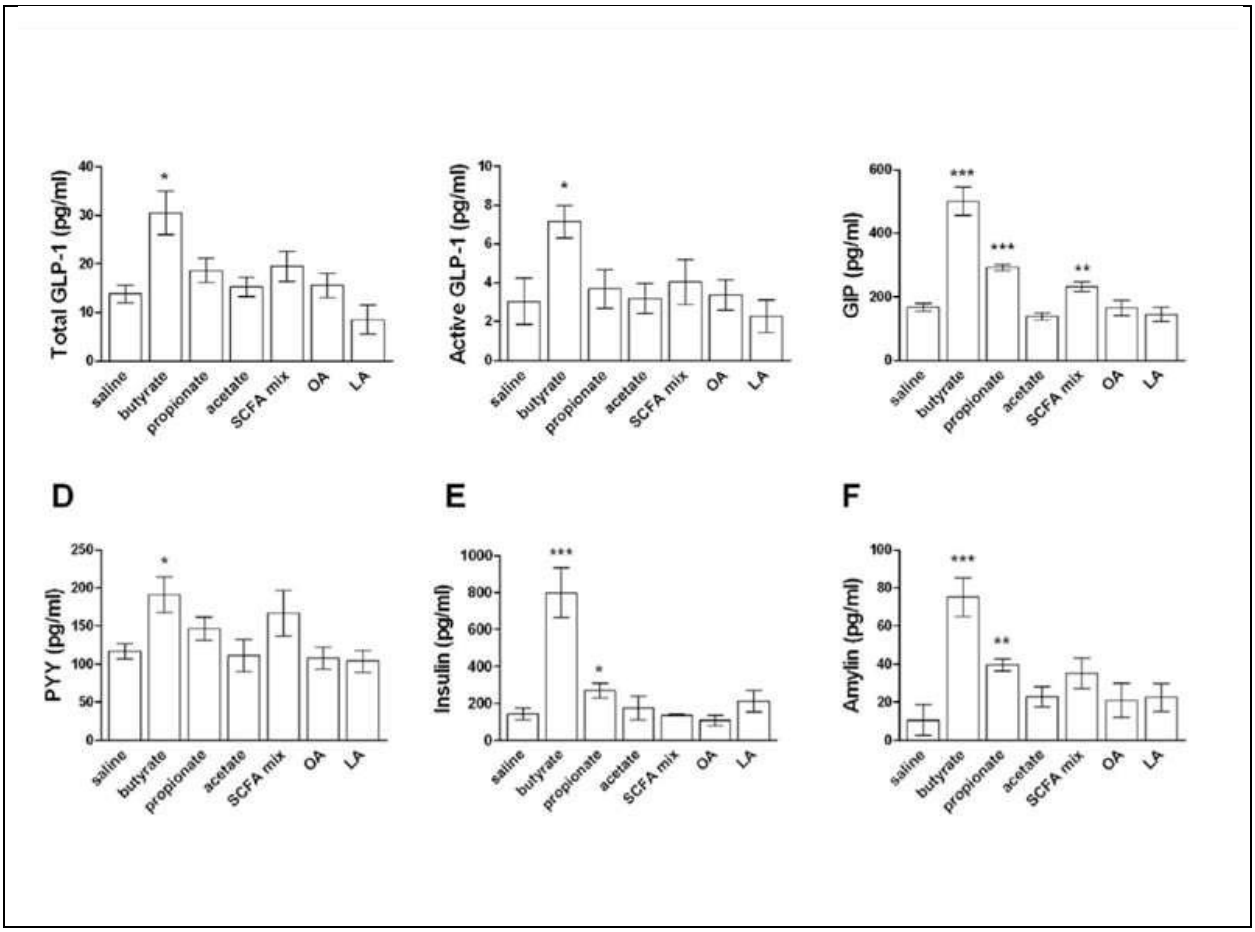
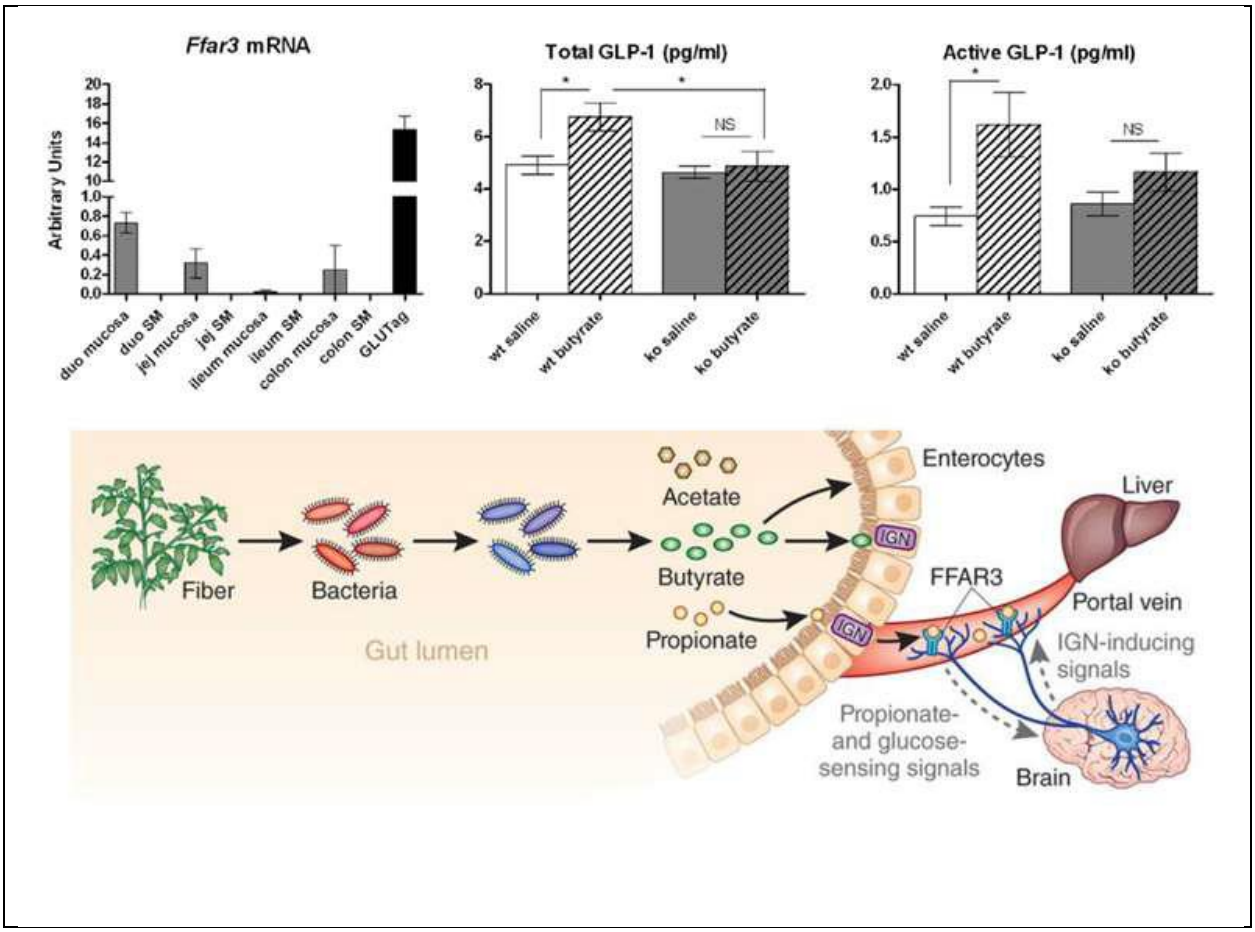
Effect of short-chain fatty acids on insulin sensitivity parameters







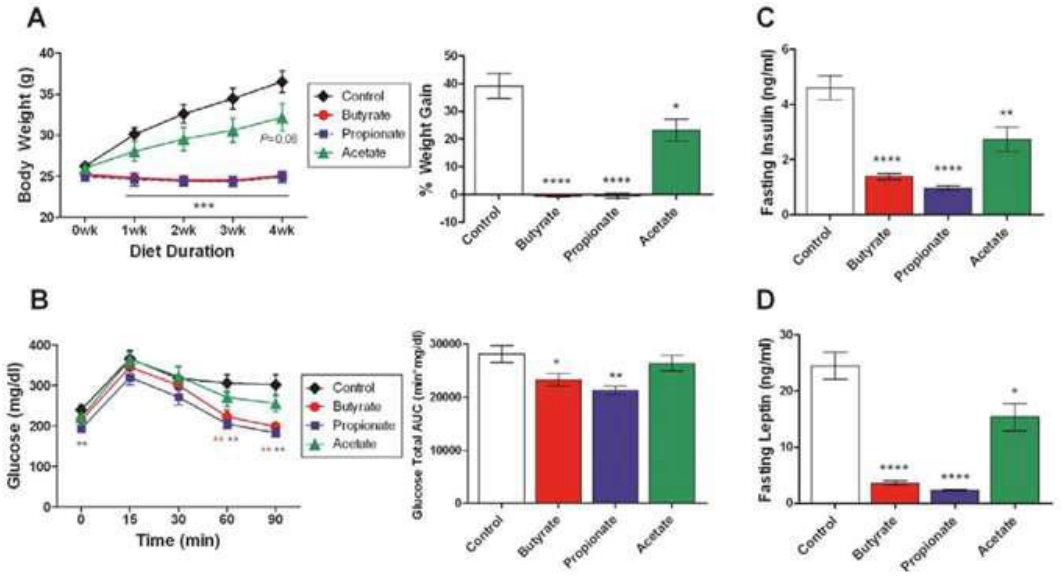

Total GLP-1 (pg/ml)
Active GLP-1 (pg/ml)
GIP (pg/ml)
D
PYY (pg/ml)
E
Insulin (pg/ml)
F
Amylin (pg/ml)
saline
butyrate
propionate
acetate
SCFA mix
OA
LA


Ffar3 mRNA
Arbitrary Units
duo mucosa
duo SM
jej mucosa
jej SM
ileum mucosa
ileum SM
colon mucosa
colon SM
GLUTag
Total GLP-1 (pg/ml)
NS
wt saline
wt butyrate
ko saline
ko butyrate
Active GLP-1 (pg/ml)
Fiber
Bacteria
Gut lumen
Acetate
Butyrate
Propionate
Enterocytes
IGN
FFAR3
Liver
Portal vein
IGN-inducing signals
Propionate- and glucose- sensing signals
Brain

Butyrate and Propionate Protect against Diet-Induced Obesity and Regulate Gut Hormones via Free Fatty Acid Receptor 3-Independent Mechanisms

(Lin et al, 2012)

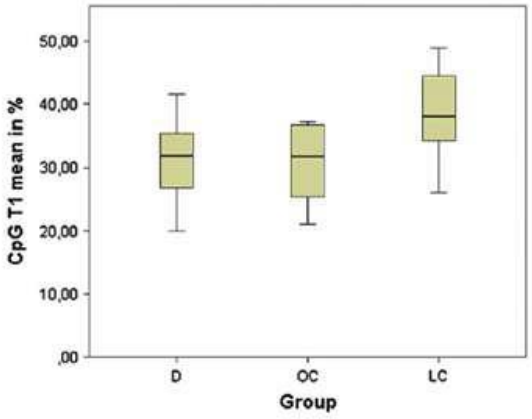
PLoS ONE 7:e35240

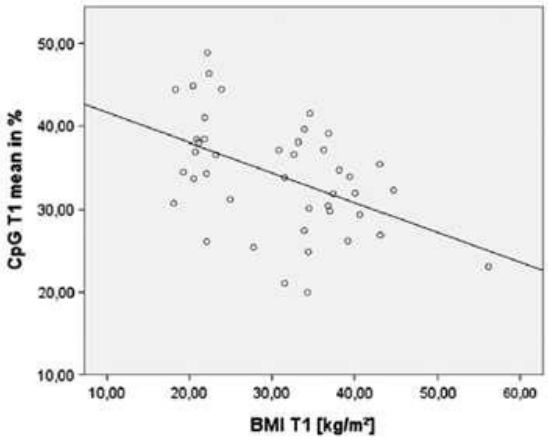


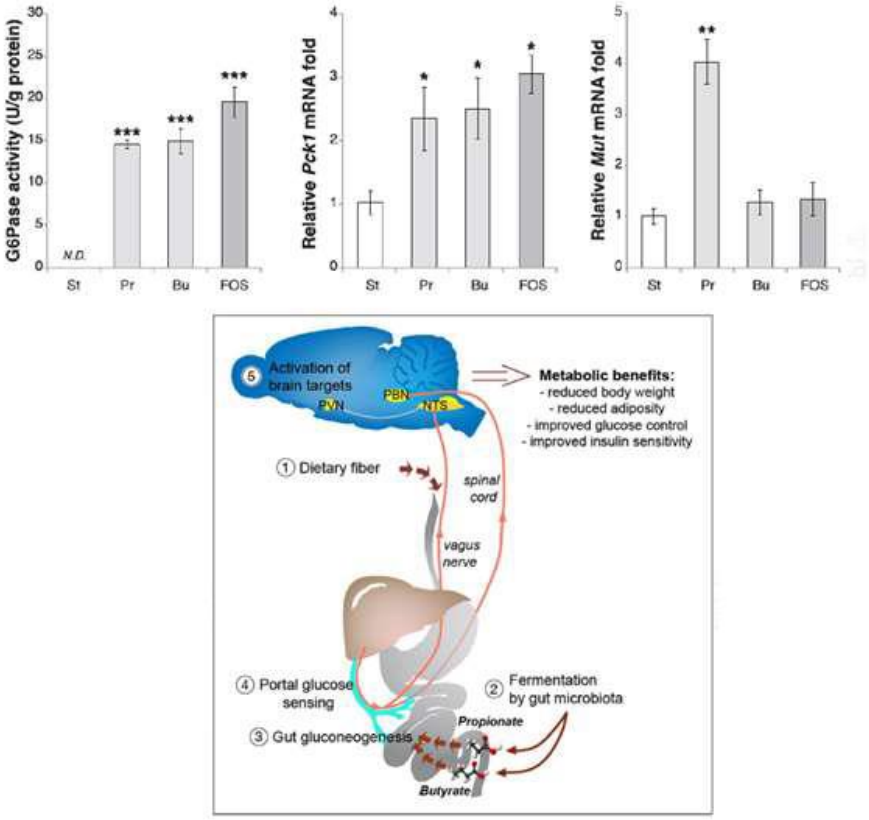
Effects of short chain fatty acid producing bacteria on epigenetic regulation of FFAR3 in type 2 diabetes and obesity

(Remely et al, 2014)

Gene 537:85-92






G6Pase activity (U/g protein)
N.D.
St
Pr
Bu
FOS
Relative Pck1 mRNA fold
Relative Mut mRNA fold
5 Activation of brain targets
PVN
PBN
NTS
Metabolic benefits:
- reduced body weight
- reduced adiposity
- improved glucose control
- improved insulin sensitivity
1 Dietary fiber
spinal cord
vagus nerve
4 Portal glucose sensing
2 Fermentation by gut microbiota
3 Gut gluconeogenesis
Propionate
Butyrate

Microbiota and metabolic syndrome
- Obesity and insulin resistance -

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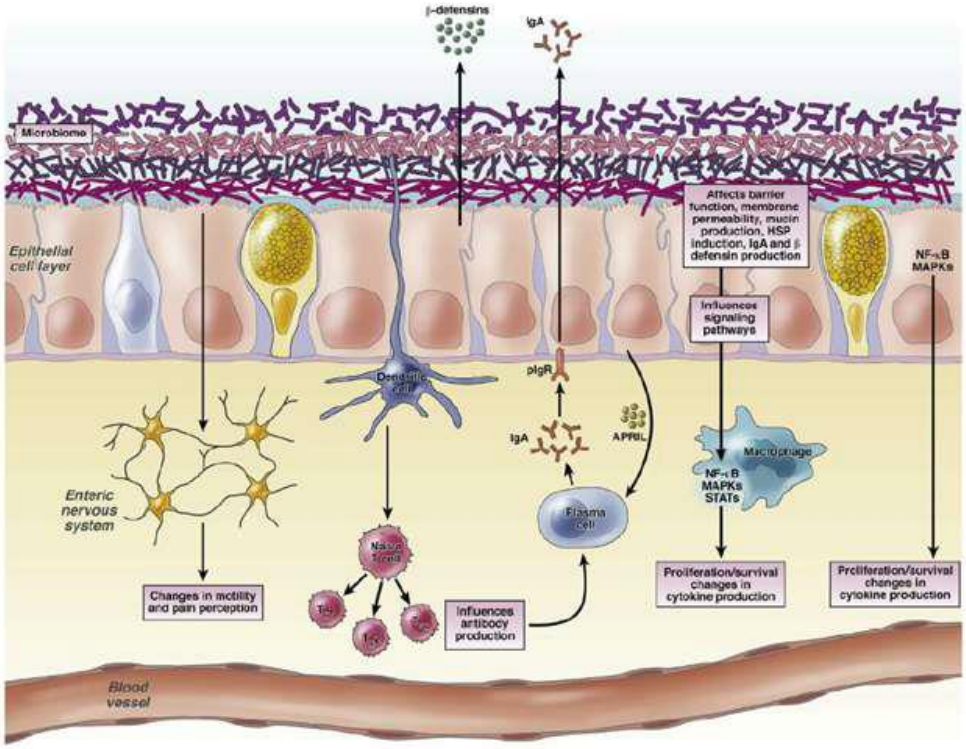
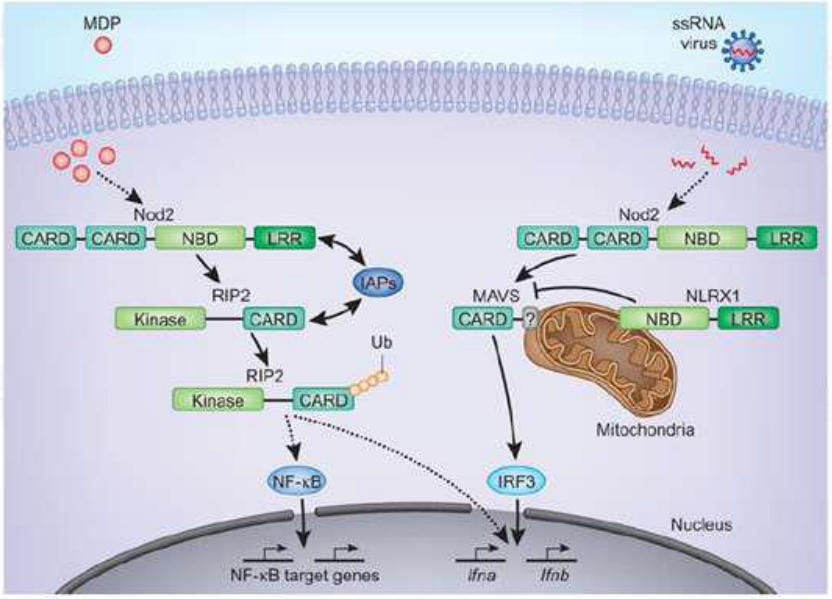
Understanding the concept of microbiota-host symbiosis



Nod2 is essential for temporal development of intestinal microbial communities

(Rehman et al, 2011)

Gut 60:1354-1362



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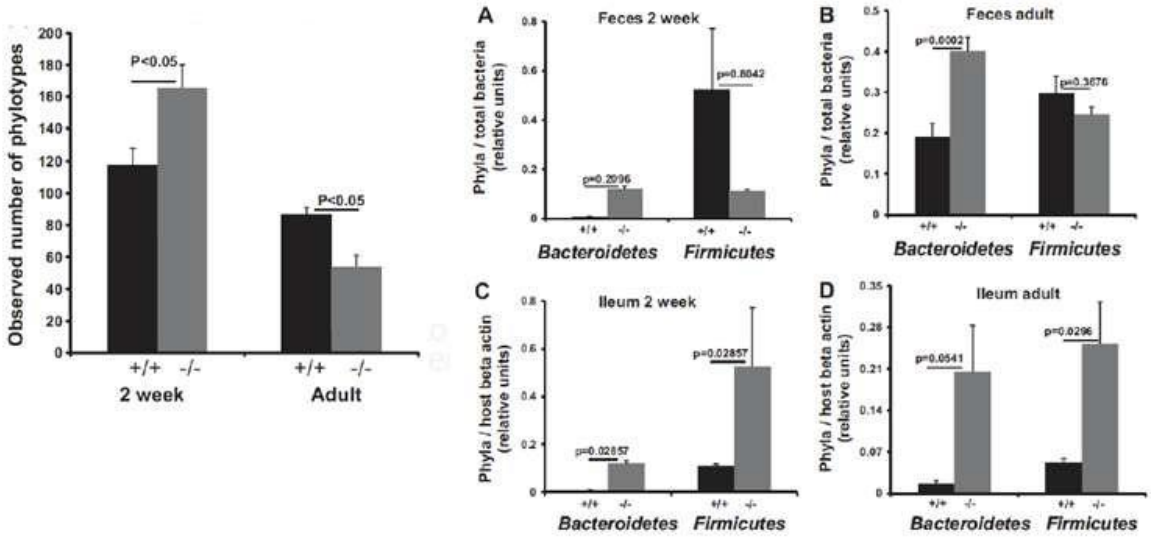

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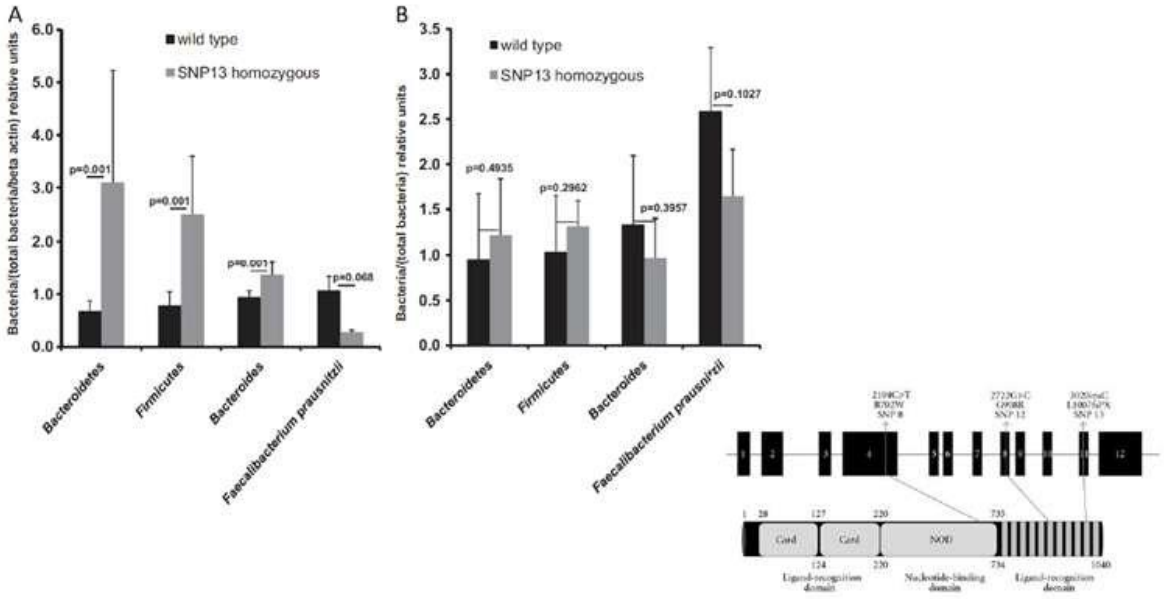
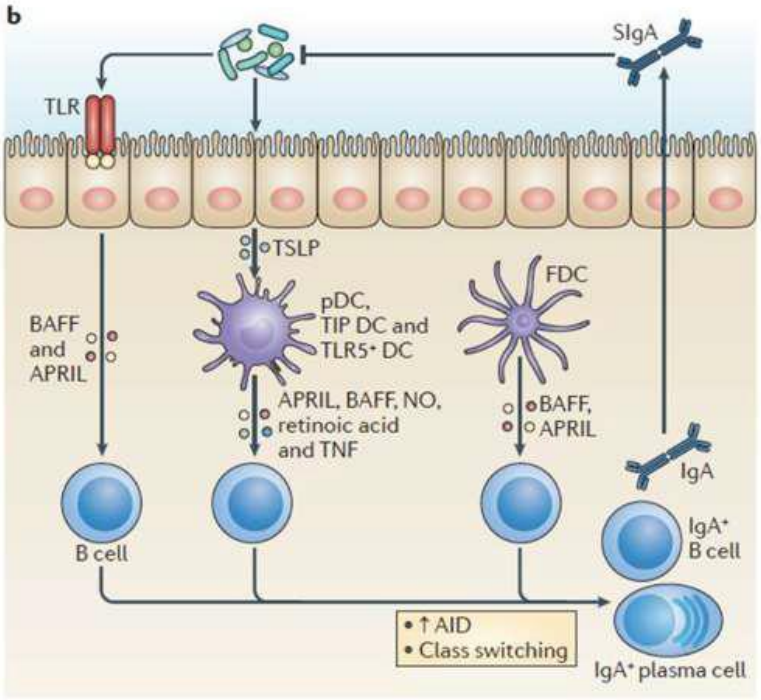
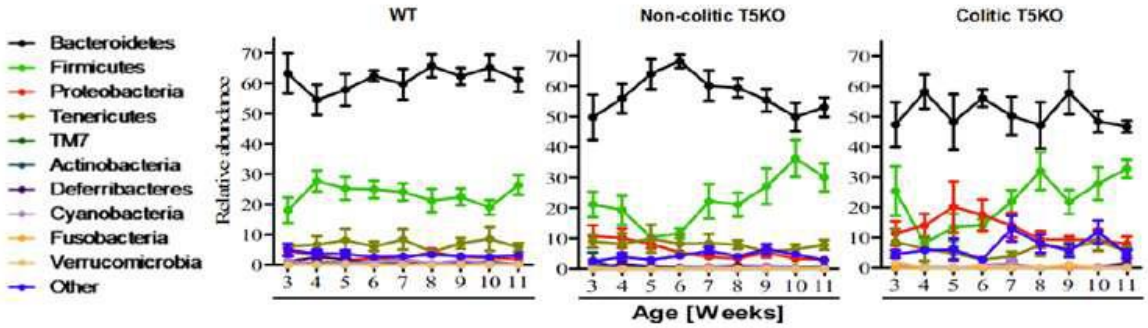
Gut 60:1354-1362




b
SIgA
TLR
TSLP
FDC
pDC,
TIP DC and
TLR5+ DC
BAFF
and
APRIL
APRIL, BAFF, NO,
retinoic acid
and TNF
BAFF,
APRIL
IgA
IgA+
B cell
B cell
• ↑ AID
• Class switching
IgA+ plasma cell

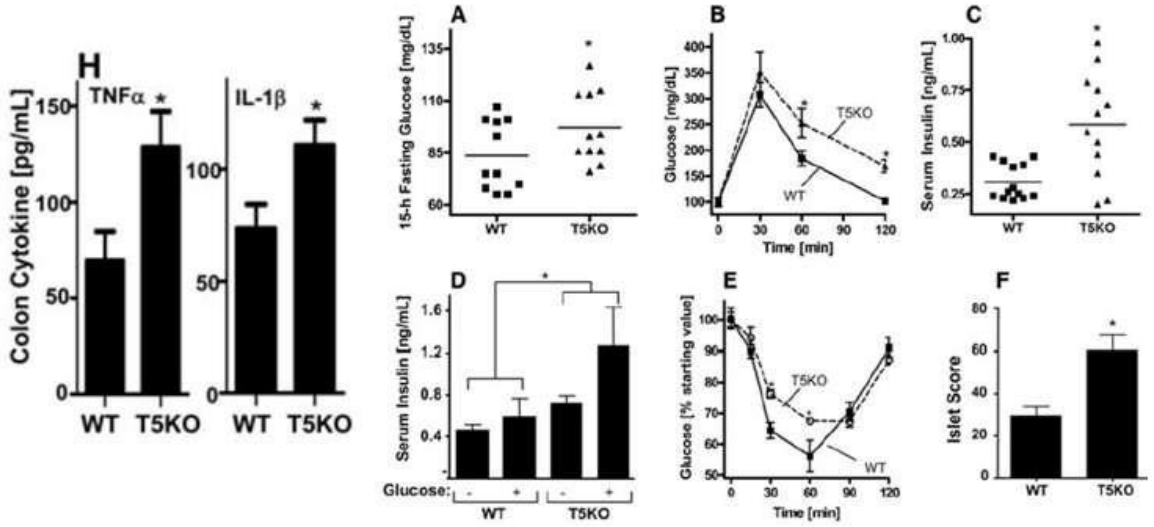
Transient inability to manage proteobacteria promotes chronic gut inflammation in TLR5-deficient mice.
(Carvalho et al, 2012)
Cell Host Microbe 12:139-152



Metabolic syndrome and altered gut microbiota in mice lacking Toll-like Receptor 5

(Vijay-Kumar et al, 2010)

Science 328;228



Metabolic syndrome and altered gut microbiota in mice lacking Toll-like Receptor 5

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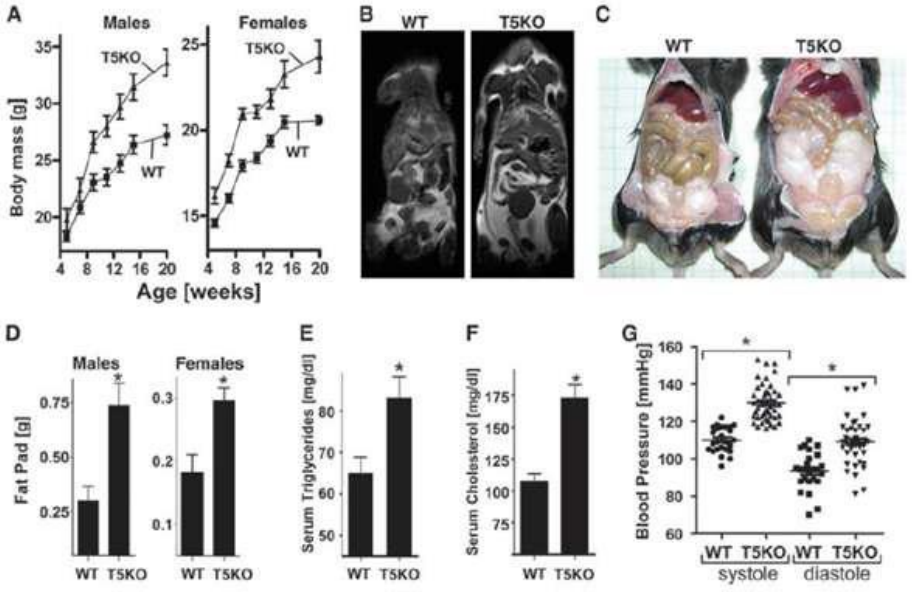
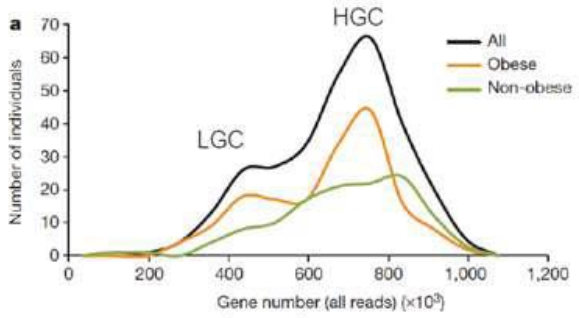
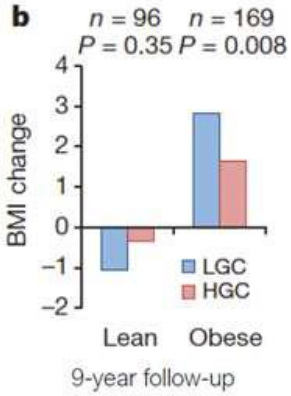
Science 328;228



Richness of human gut microbiome correlates with metabolic markers

(Le Chatelier et al, 2013)
Nature 500:541.





	LGC	HGC
N (men/women)	68 (23/45)	224 (113/111)
Age (years)	55 (50–62)	57 (50–61)
[redacted]		
Whole body fat (%)	37 (29–42)	31 (25–39)
S-insulin (pmol l^{-1})	50 (35–91)	44 (26–66)
HOMA-IR	1.9 (1.2–3.3)	1.6 (0.9–2.6)
P-triglycerides (mmol l^{-1})	1.32 (0.97–1.76)	1.15 (0.82–1.57)
P-free fatty acids (mmol l^{-1})	0.55 (0.39–0.70)	0.48 (0.35–0.60)
P-ALT (U l^{-1})	20 (14–30)	19 (15–26)
S-leptin (μg l^{-1})	17.0 (6.7–32.6)	8.3 (3.4–26.4)
S-adiponectin (mg l^{-1})	7.5 (5.5–12.9)	9.6 (6.7–13.7)
B-leucocytes (10^9 l^{-1})	6.4 (5.2–7.8)	5.6 (4.8–6.9)
[redacted]		

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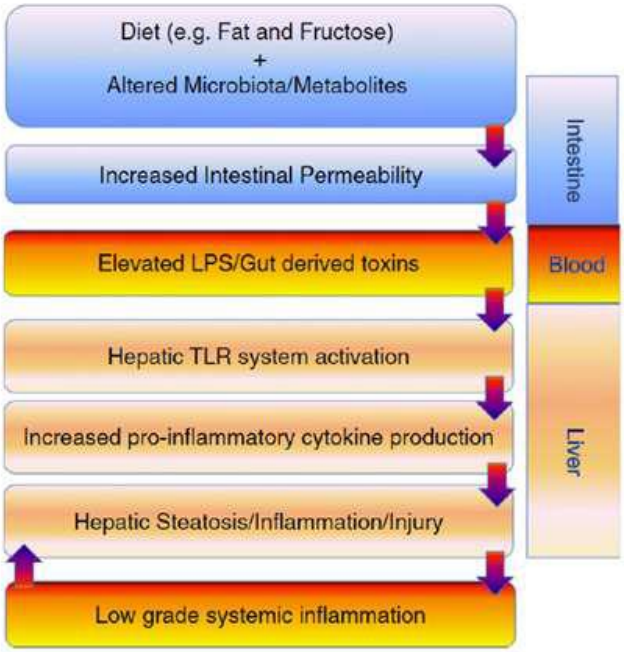
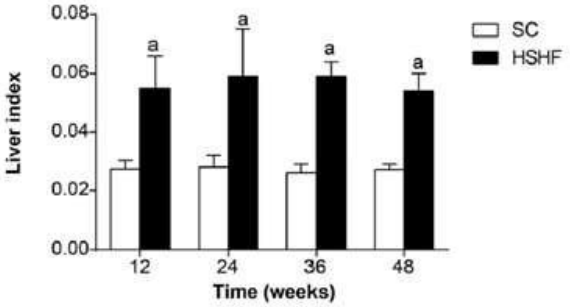
Gut-liver axis and non-alcoholic fatty liver disease (NAFLD)

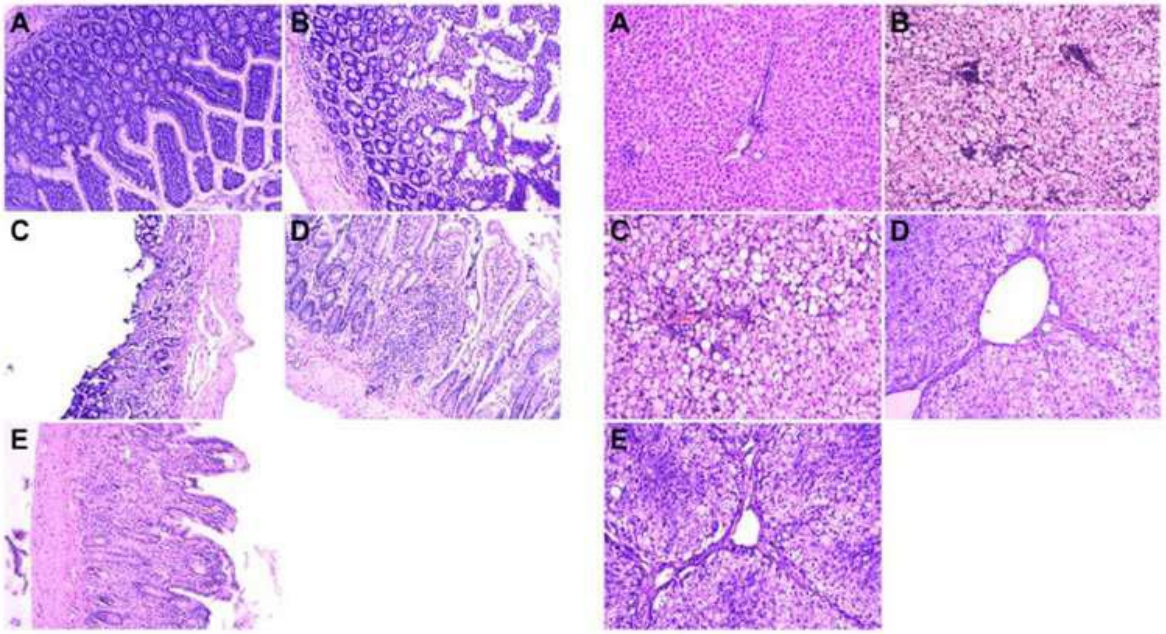


A model of metabolic syndrome and related diseases with intestinal endotoxemia in rats fed a high fat and high sucrose diet.

(Zhou et al, 2014)
PLoS One, 9:e115148



Indexes	Groups	12th week	24th week	36th week	48th week
LPS, EU/ml	SC	0.07±0.01	0.07±0.01	0.08±0.01	0.08±0.01
	HSHF	0.67±0.07[a]	0.73±0.09[a]	0.74±0.07[a]	0.74±0.08 [a]
ALP, U/gprot	SC	0.015±0.008	0.019±0.007	0.02±0.013	0.019±0.016
	HSHF	0.05±0.017[a]	0.073±0.02[a]	0.075±0.02[a]	0.075±0.024[a]
TNFα, ng/ml	SC	1.09±0.21	1.02±0.13	7.24±1.48	6.56±3.5
	HSHF	2.01±0.75[a]	2.1±0.31[a]	1.96±0.31 [a]	1.93±0.30[a]
TNFα in pancreas, ng/ml	SC	0.02±0.01	0.02±0.004	0.019±0.01	0.018±0.005
	HSHF	0.02±0.01	0.03±0.02	0.15±0.04 [abc]	0.17±0.045 [abc]
TNFα in fat, ng/ml	SC	0.022±0.01	0.017±0.004	0.019±0.003	0.016±0.004
	HSHF	0.063±0.01 [a]	0.094±0.01 [ab]	0.166±0.027 [abc]	0.18±0.031 [abc]
IL-6, pg/ml	SC	0.11±0.05	0.10±0.21	0.10±0.014	0.11±0.013
	HSHF	0.18±0.03[a]	0.24±0.03[a]	0.24±0.041[a]	0.25±0.042[a]


A
B
C
D
E
A
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E

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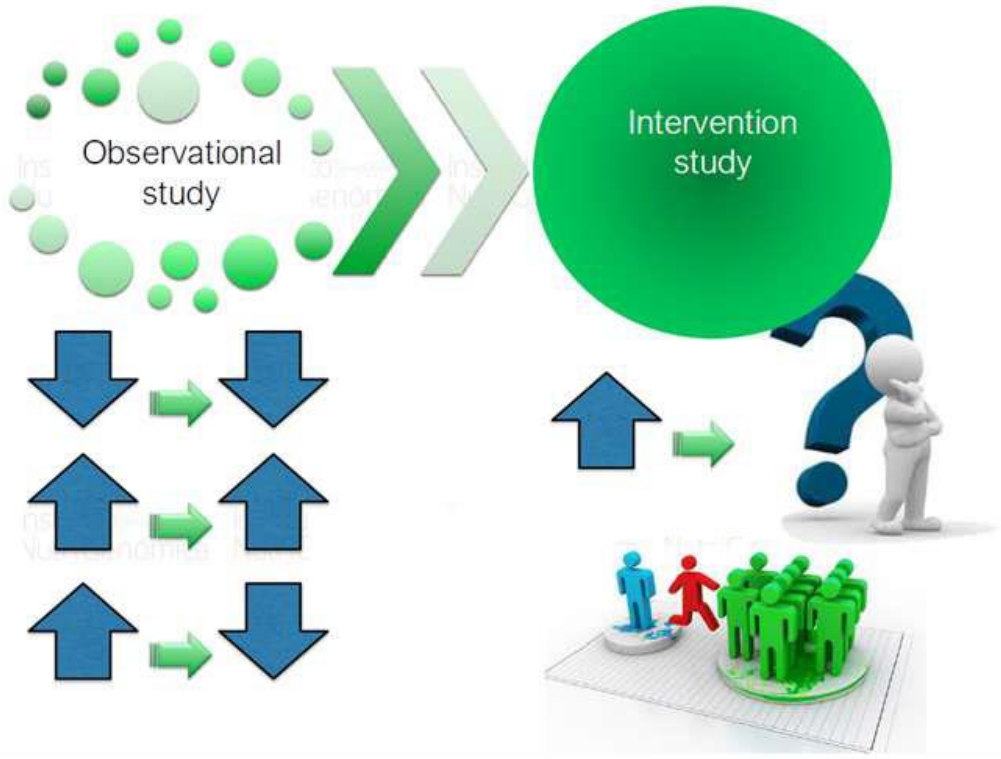
Current information constraints



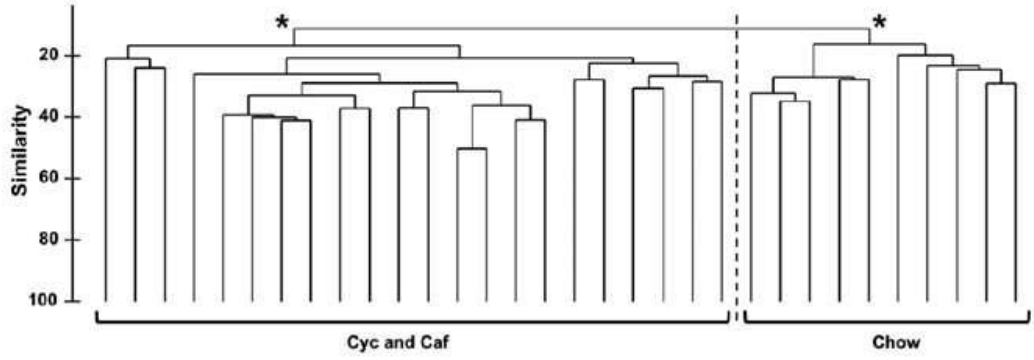
Alternating or continuous exposure to cafeteria diet leads to similar shifts in gut microbiota compared to chow diet

(Kaakoush et al, 2016)

Mol Nutr Food Res

Family	Chow	Caf	Cyc
Lachnospiraceae	32.35	30.60	44.46
Coriobacteriaceae	0.87	6.13	6.97
Ruminococcaceae	26.24	27.50	20.41
Enterobacteriaceae	17.00	0.25	1.53
Bacteroidaceae	0.26	6.24	2.82
Porphyromonadaceae	1.99	7.04	4.85
Prevotellaceae	0.96	2.17	1.99
Peptostreptococcaceae	0.51	1.54	0.68

Genus	Chow	Caf	Cyc
Blautia	0.19	10.77	22.97
Collinsella	0.00	5.93	6.37
Ruminococcus	0.17	10.36	1.90
Escherichia_Shigella	12.80	0.04	1.32
Bacteroides	0.26	6.24	2.82
Parabacteroides	0.28	1.74	2.16
Prevotella	0.89	1.69	1.89
Lachnospiracea_incertae_sedis	0.71	2.65	2.51
Clostridium_XI	0.49	1.54	0.63
Roseburia	0.31	0.61	0.84



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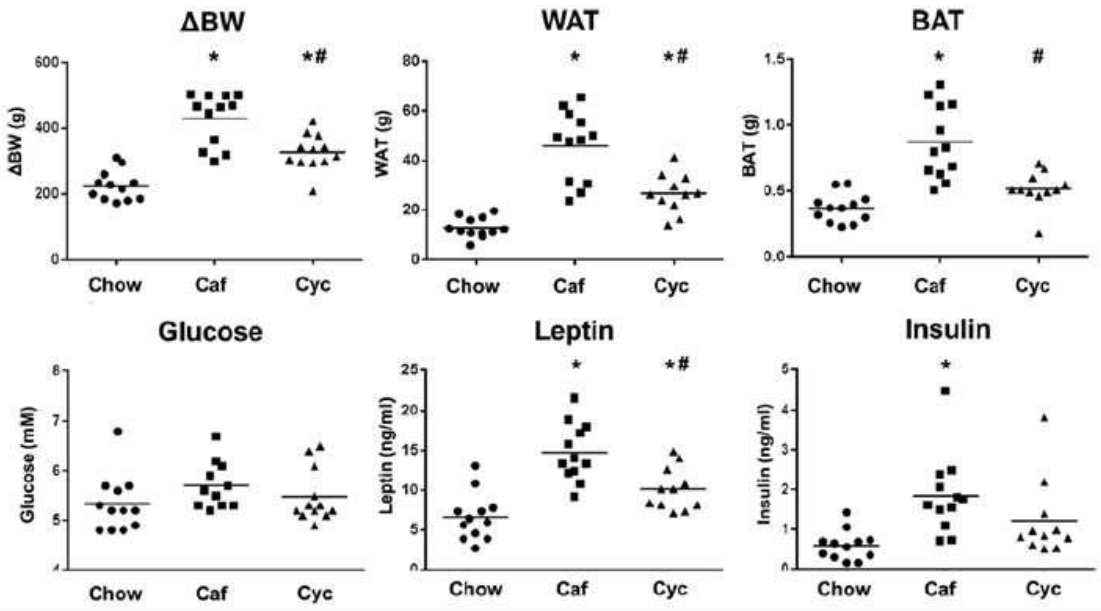
Mol Nutr Food Res



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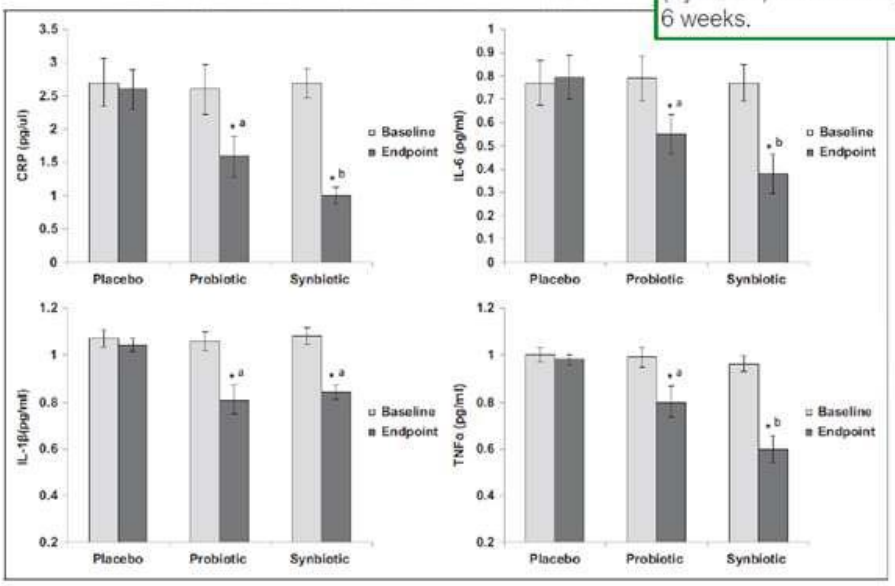
Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study

(Rajkumar et al, 2015)

J Cardiovasc Pharmacol Ther 20:289-98

(Placebo) gelatine,
(Probiotic) $2x10^9$ CFUs L .salivarius
(Synbiotic) L salivarius y FOS (10 g/d)
6 weeks.



Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with type 2 diabetes

(Asemi et al, 2013)

Ann Nutr Metab 63:1-9

1. Lactobacillus acidophilus (2 × 10(9) CFU),
2. L. casei (7 × 10(9) CFU),
3. L. rhamnosus (1.5 × 10(9) CFU),
4. L. bulgaricus (2 × 10(8) CFU),
5. Bifidobacterium breve (2 × 10(10) CFU),
6. B. longum (7 × 10(9) CFU),
7. Streptococcus thermophilus (1.5 × 10(9) CFU)

	Placebo (n = 27)				Probiotic supplement (n = 27)				p^b
	week 0	week 8	change	p^a	week 0	week 8	change	p^a	
FPG, mg/dl	134.5±9.6	163.3±12	28.8±8.5	0.002	143.8±10.7	145.4±9.5	1.6±6	0.80	0.01
$HbA1_C$, %	6.35±0.3	6.53±0.28	0.18±0.31	0.55	7.71±0.37	7.41±0.41	−0.3±0.37	0.42	0.32
Insulin, µIU/ml	5.82±1	9.93±1.51	4.11±0.91	<0.0001	5.7±0.8	7.74±1.11	2.04±0.82	0.02	0.09
HOMA-IR	2.03±0.44	4.41±0.88	2.38±0.65	0.001	1.98±0.33	2.76±0.44	0.78±0.31	0.02	0.03
Total cholesterol, mg/dl	164.6±10.1	177.8±6.6	13.2±8.9	0.15	171.3±9.4	176.2±7.4	4.9±6.9	0.48	0.46
Triglycerides, mg/dl	134±11.7	150.2±11.6	16.2±11.5	0.17	159.5±15.2	160.3±13.7	0.8±10.5	0.93	0.33
LDL-C, mg/dl	84.2±7.5	102.8±5.9	18.6±6.6	0.009	83.4±6.3	97.4±6.4	14±4.6	0.006	0.56
HDL-C, mg/dl	53.6±2.8	44.9±1.7	−8.7±2.2	0.001	56±3	46.8±2	−9.2±2.3	<0.0001	0.83
Total:HDL-C ratio	3.1±0.2	4±0.2	0.9±0.15	<0.0001	3±0.1	3.8±0.2	0.8±0.1	<0.0001	0.30
Hs-CRP, ng/ml	2,107.75±361.79	2,986.47±652.09	878.72±586.44	0.14	2,793.42±617.2	2,015.85±380.16	−777.57±441.7	0.09	0.02
TAC, mmol/l	870.06±30.75	955±28.06	84.94±24.32	0.002	925.3±41.59	1,005.27±40.49	79.97±41.8	0.06	0.91
GSH, µmol/l	750.5±60.72	717.04±40.06	−33.46±69.54	0.63	832.96±68.95	1,073.59±65.76	240.63±101.29	0.02	0.03
Uric acid, mg/dl	4.73±0.27	4.88±0.24	0.15±0.21	0.47	4.71±0.27	5.51±0.28	0.8±0.27	0.008	0.07

Effect of Probiotic (VSL#3) and Omega-3 on Lipid Profile, Insulin Sensitivity, Inflammatory Markers, and Gut Colonization in Overweight Adults: A Randomized, Controlled Trial

(Rajkumar et al, 2014)

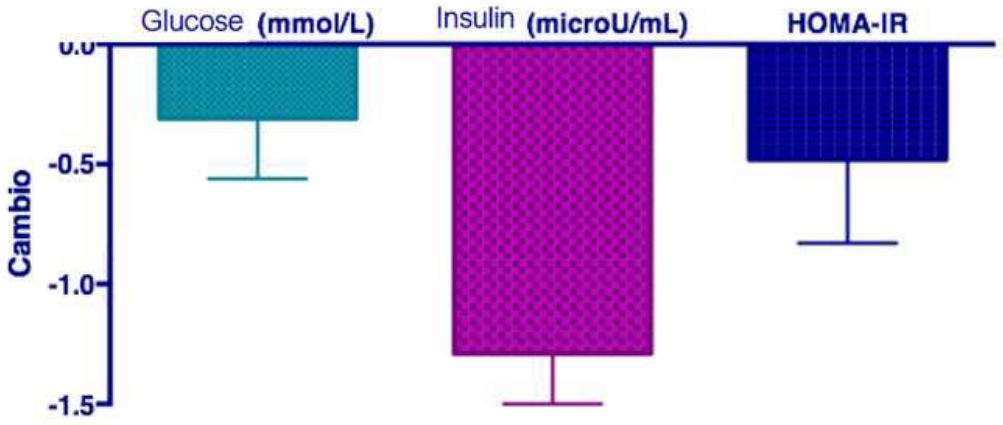
Mediators of Inflammation, 2014:348959

VSL#3 (manufactured in India by Sun Pharmaceutical Ind. Ltd.) is a freeze-dried pharmaceutical probiotic preparation containing 112.5 × 109 CFU/capsule of three strains of bifidobacteria (*Bifidobacterium longum*, *Bifidobacterium infantis*, and *Bifidobacterium breve*), four strains of lactobacilli (*Lactobacillus acidophilus*, *Lactobacillus paracasei*, Lactobacillus *delbrueckii* subsp. *bulgaricus*, and *Lactobacillus plantarum*), and one strain of *Streptococcus salivarius* subsp. *thermophilus*

	Placebo		Probiotic		Omega-3		Probiotic + omega-3	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Fasting blood glucose (mg/dL)	89.30 ± 3.3	91.92 ± 3.18^{*a}	88 ± 1.01	79.38 ± 1.05^{*b}	87.60 ± 1.4	83.93 ± 1.23^{*c}	86.70 ± 2.15	74.46 ± 1.188^{*cd}
Cholesterol (mg/dL)	197.80 ± 13.92	197.91 ± 13.93^{a}	165.10 ± 5.76	156.06 ± 5.85^{*a}	165.50 ± 9.73	161.06 ± 9.74^{*a}	215.10 ± 7.86	204.46 ± 7.73^{*a}
Triglyceride (mg/dL)	128 ± 2.26	128.85 ± 27.7^{a}	140.70 ± 17.6	133.13 ± 17.39^{*ab}	105.90 ± 6.53	102.62 ± 6.44^{*a}	150.00 ± 8.49	138.74 ± 8.35^{*b}
LDL (mg/dL)	136.30 ± 14.19	136.67 ± 14.2^{a}	102.80 ± 4.91	94.50 ± 4.31^{b}	106.10 ± 10.1	99.87 ± 10.08^{*b}	150.30 ± 8.41	134.58 ± 7.93^{*a}
HDL (mg/dL)	35.90 ± 2.85	35.46 ± 2.85^{a}	29.60 ± 1.12	34.93 ± 1.08^{*a}	38.20 ± 1.65	40.66 ± 1.62^{*b}	34.80 ± 2.23	42.13 ± 1.89^{*b}
VLDL (mg/dL)	25.60 ± 5.45	25.77 ± 5.54^{a}	32.60 ± 4.38	26.62 ± 3.47^{a}	21.10 ± 1.3	20.51 ± 1.28^{*a}	30.00 ± 1.69	27.74 ± 1.67^{*a}
Atherogenic factor	196.80 ± 13.92	196.91 ± 13.93^{a}	164.10 ± 5.76	155.75 ± 5.8^{a}	164.50 ± 9.73	160.06 ± 9.74^{*a}	214.10 ± 7.86	203.46 ± 7.73^{*a}
Insulin level (μU/mL)	17.90 ± 0.52	18.26 ± 0.43^{a}	18.40 ± 0.27	17.59 ± 0.28^{*b}	18.50 ± 0.23	17.84 ± 0.22^{*a}	18.00 ± 0.3	16.75 ± 0.25^{*b}
Insulin resistance	3.90 ± 0.1	4.11 ± 0.12^{*a}	4.00 ± 0.03	3.44 ± 0.04^{*b}	4.00 ± 0.08	3.69 ± 0.07^{*c}	3.80 ± 0.08	3.07 ± 0.04^{*d}
CRP (mg/L)	5.30 ± 0.58	5.35 ± 0.58^{*a}	5.60 ± 0.52	4.36 ± 0.49^{*a}	5.60 ± 0.74	5.26 ± 0.72^{*a}	6.20 ± 0.41	4.22 ± 0.41^{*a}

	Placebo		Probiotic		Omega-3		Pro + Omega-3	
	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment	Pretreatment	Posttreatment
Total bacteria	7.74 ± 0.21	7.71 ± 0.18^{a}	8.77 ± 0.09	9.13 ± 0.18^{*b}	7.7 ± 0.19	7.78 ± 0.16^{a}	8.83 ± 0.09	9.55 ± 0.12^{**b}
Total anaerobes	9.32 ± 0.17	9.27 ± 0.12^{a}	9.66 ± 0.06	10.71 ± 0.07^{**b}	9.44 ± 0.18	9.54 ± 0.09^{a}	9.61 ± 0.1	10.86 ± 0.05^{**b}
Lactobacillus	6.87 ± 0.12	6.86 ± 0.14^{a}	6.77 ± 0.1	7.95 ± 0.13^{**b}	6.76 ± 0.26	6.8 ± 0.12^{a}	6.76 ± 0.12	7.96 ± 0.12^{**b}
Bifidobacteria	8.89 ± 0.17	8.88 ± 0.14^{a}	8.71 ± 0.11	9.94 ± 0.01^{**b}	8.71 ± 0.08	8.75 ± 0.17^{a}	8.71 ± 0.08	9.9 ± 0.03^{**b}
Streptococcus	2.81 ± 0.21	2.80 ± 0.31^{a}	2.66 ± 0.1	8.96 ± 0.16^{**b}	2.67 ± 0.19	2.89 ± 0.29^{a}	2.67 ± 0.11	8.99 ± 0.13^{**b}
Coliform	6.82 ± 0.19	6.83 ± 0.13^{a}	6.59 ± 0.1	6.35 ± 0.2^{a}	6.54 ± 0.13	6.44 ± 0.12^{a}	6.99 ± 0.14	6.58 ± 0.11^{**a}
E.coli	6.59 ± 0.14	6.93 ± 0.19^{**a}	6.58 ± 0.09	6.47 ± 0.13^{b}	6.55 ± 0.18	6.53 ± 0.09^{a}	6.69 ± 0.19	6.39 ± 0.09^{b}
Bacteroides	6.61 ± 0.19	6.98 ± 0.15^{**a}	6.99 ± 0.18	7.57 ± 0.17^{**b}	6.59 ± 0.1	6.45 ± 0.25^{c}	6.96 ± 0.15	7.87 ± 0.11^{**d}

Effect of probiotics on glycemic control: a systematic review and meta-analysis of randomized, controlled trials.
(Ruan et al, 2015)
PlosOne 10:e0132121



Probiotic intervention has strain-specific anti-inflammatory effects in healthy adults

(Kekkonen et al, 2008)

World J Gastroenterol. 14:2029-36

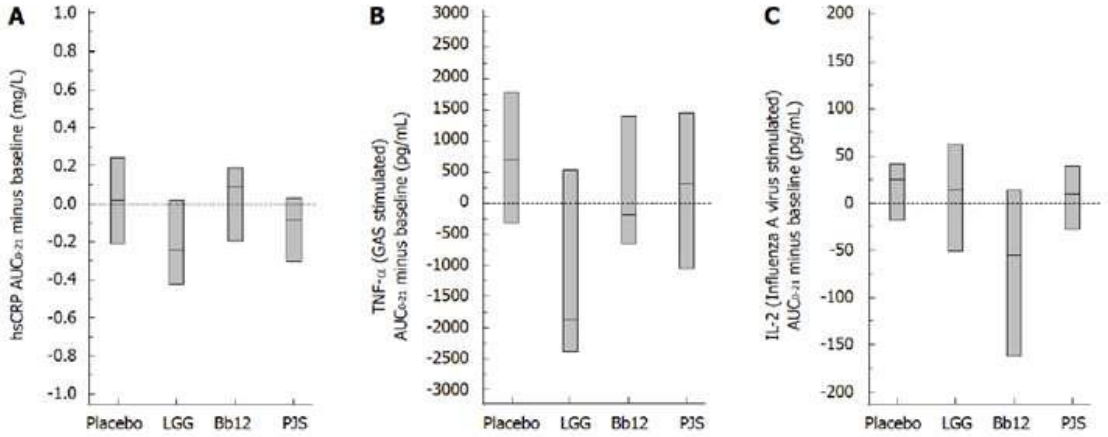
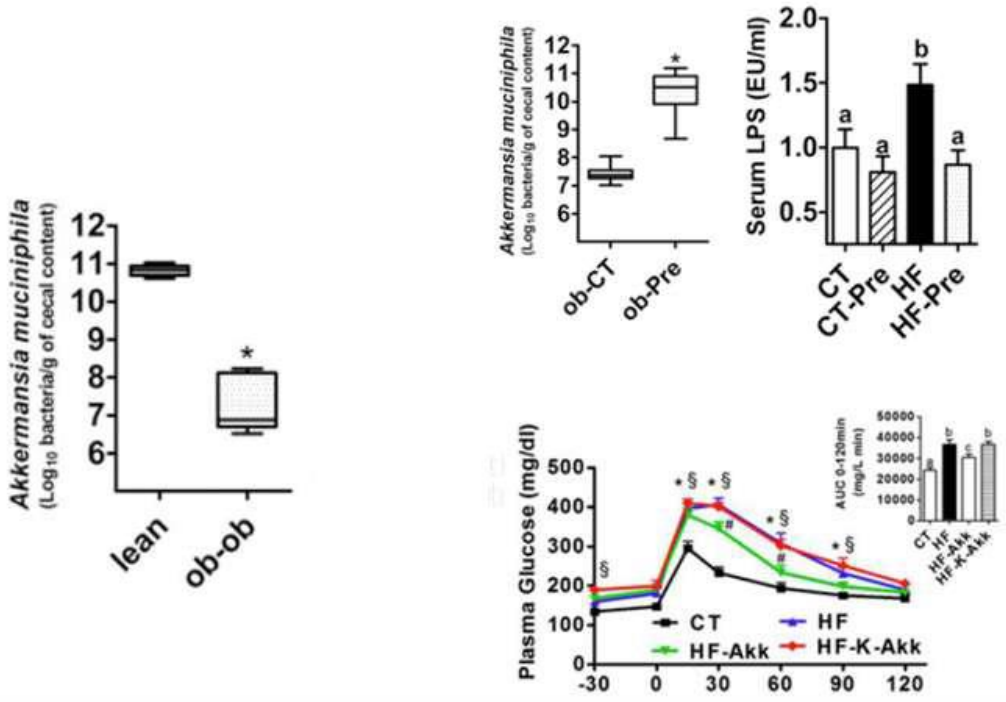


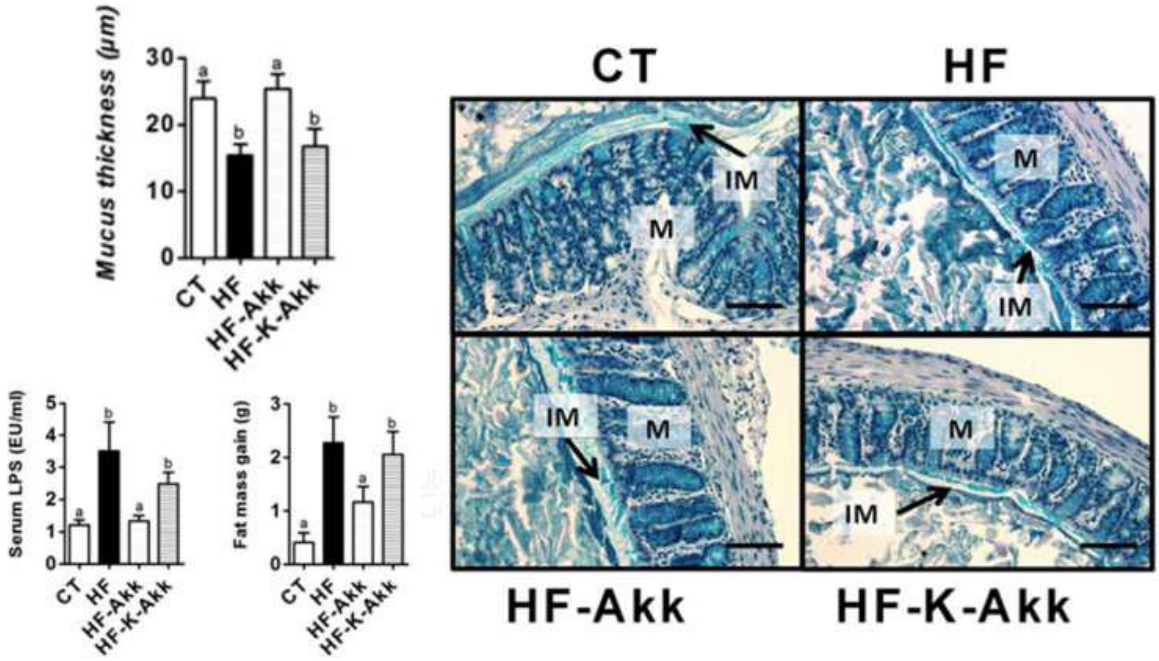
Figure 1 The median AUC_{0-21} (minus baseline) with IQR for serum highly sensitive CRP (hsCRP) levels (**A**), for *Streptococcus pyogenes* (GAS) -stimulated TNF-α production from peripheral blood mononuclear cells (**B**) and for Influenza A virus-stimulated IL-2 production from peripheral blood mononuclear cells (**C**) during the 3-wk intervention period in healthy adults (n = 62). LGG: *Lactobacillus rhamnosus* GG; Bb12: *Bifidobacterium animalis* ssp. lactis Bb12; PJS: *Propionibacterium freudenreichii* ssp. *shermanii* JS.

Cross-talk between *Akkermansia muciniphila* and intestinal epithelium controls diet-induced obesity

(Everard et al, 2013)

PNAS 111:9066-9071




Mucus thickness (μm)
30
20
10
0
a
b
a
b
CT
HF
HF-Akk
HF-K-Akk
Serum LPS (EU/ml)
5
4
3
2
1
0
a
b
a
b
CT
HF
HF-Akk
HF-K-Akk
Fat mass gain (g)
3
2
1
0
a
b
a
b
CT
HF
HF-Akk
HF-K-Akk
CT
HF
IM
M
M
IM
IM
M
M
IM
HF-Akk
HF-K-Akk

Microbiota and metabolic syndrome
- Obesity and insulin resistance -

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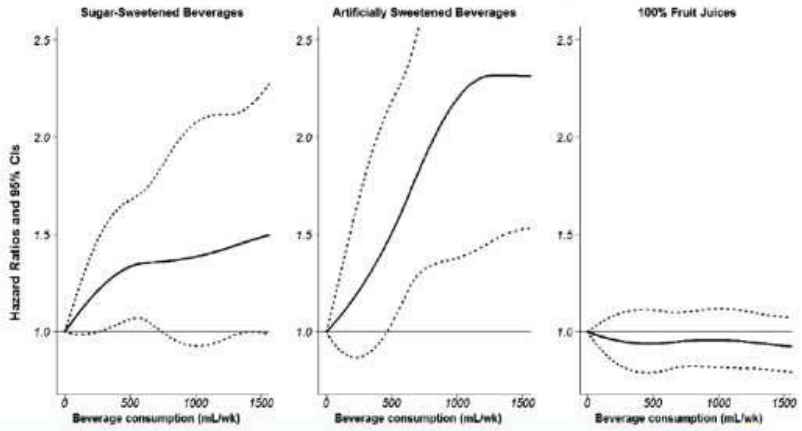
Consumption of artificially and sugar-sweetened beverages and incident type 2 diabetes in the Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale-European Prospective Investigation into Cancer and Nutrition cohort

(Fagherazzi et al, 2013)

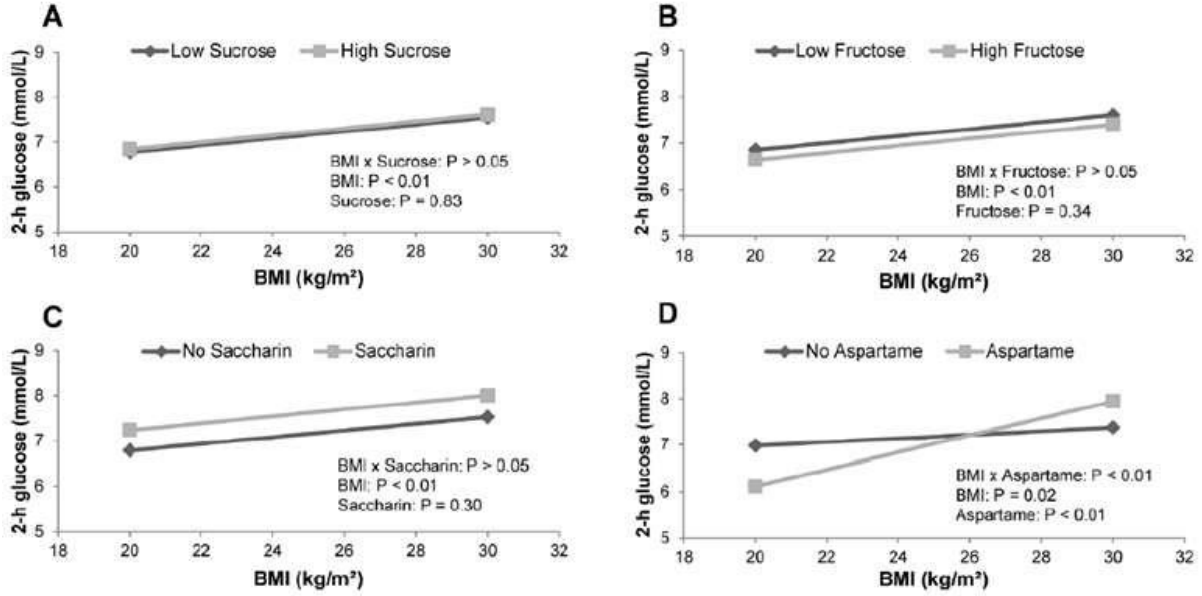
Am J Clin Nutr 97:517-523



Aspartame intake is associated with greater glucose intolerance in individuals with obesity

(Kuk & Brown, 2016)

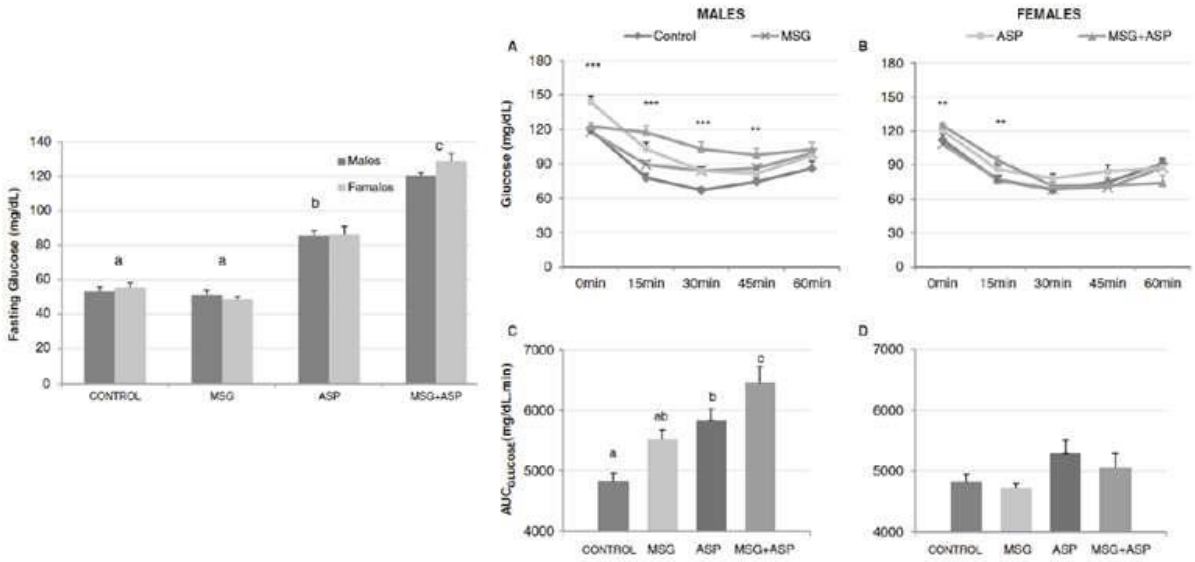
Appl Physiol Nutr Metab 41:795-798



Interactive effects of neonatal exposure to monosodium glutamate and aspartame on glucose homeostasis

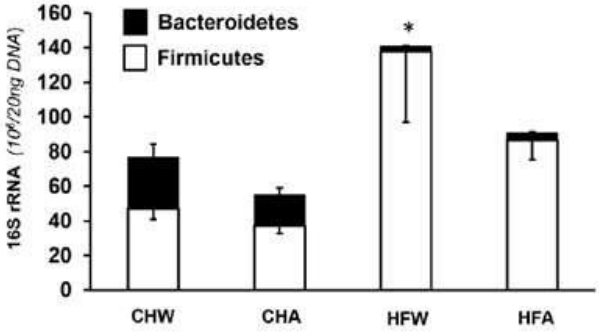
(Collison et al, 2012)

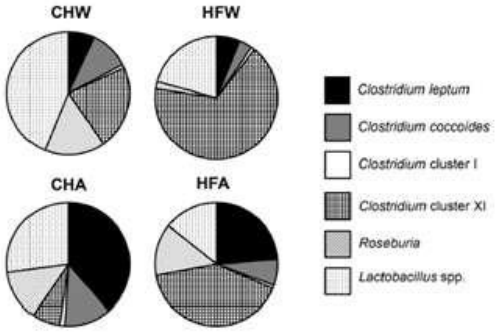
Nutr Metab 9:58

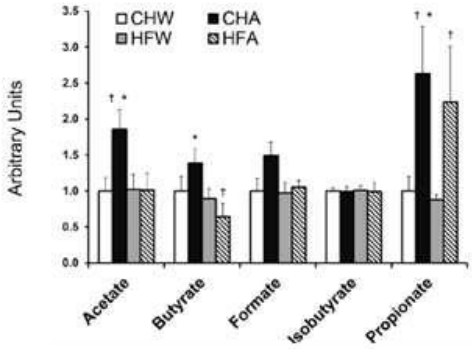


Low-Dose Aspartame Consumption Differentially Affects Gut Microbiota-Host Metabolic Interactions in the Diet-Induced Obese Rat

(Palmnäs et al, 2014)
PLoS One 9:e109841





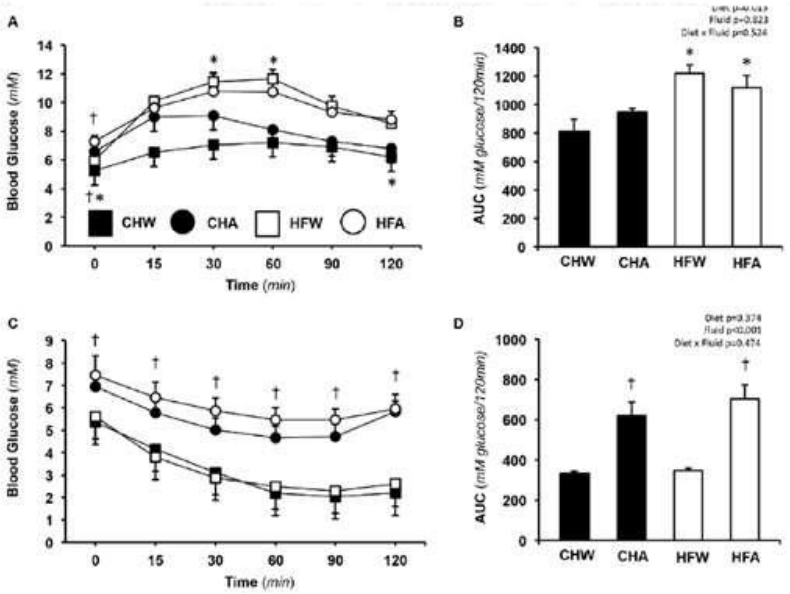


Low-Dose Aspartame Consumption Differentially Affects Gut Microbiota-Host Metabolic Interactions in the Diet-Induced Obese Rat

(Palmnäs et al, 2014)

PLoS One 9:e109841

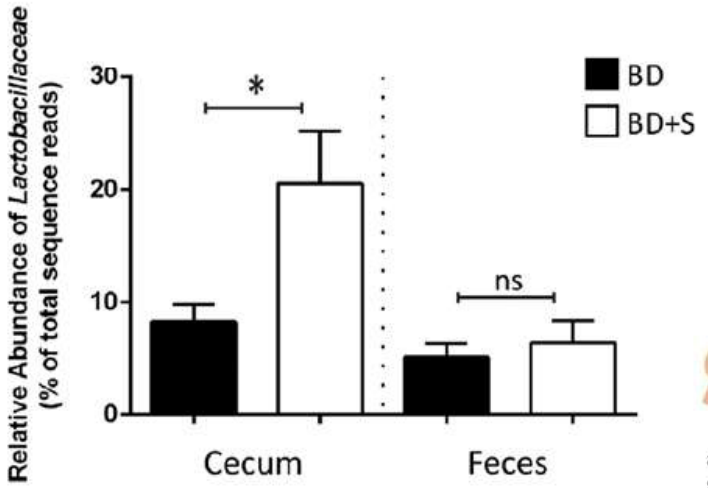
Aspartame



Low calorie sweeteners and gut microbiota

(Daly et al, 2016)

Physiology and behavior.



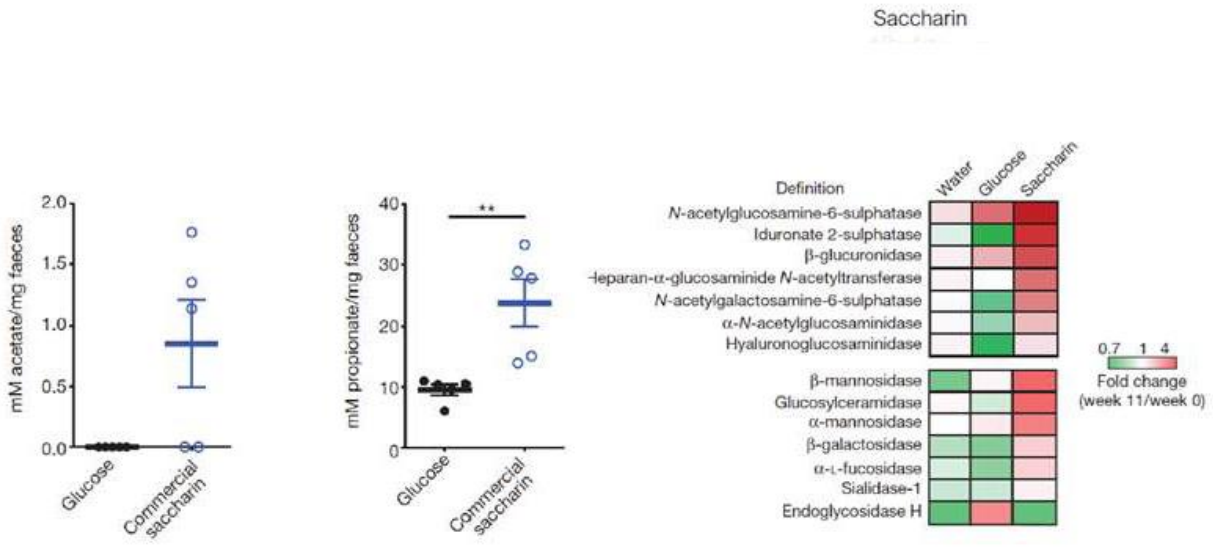
SUCRAM®

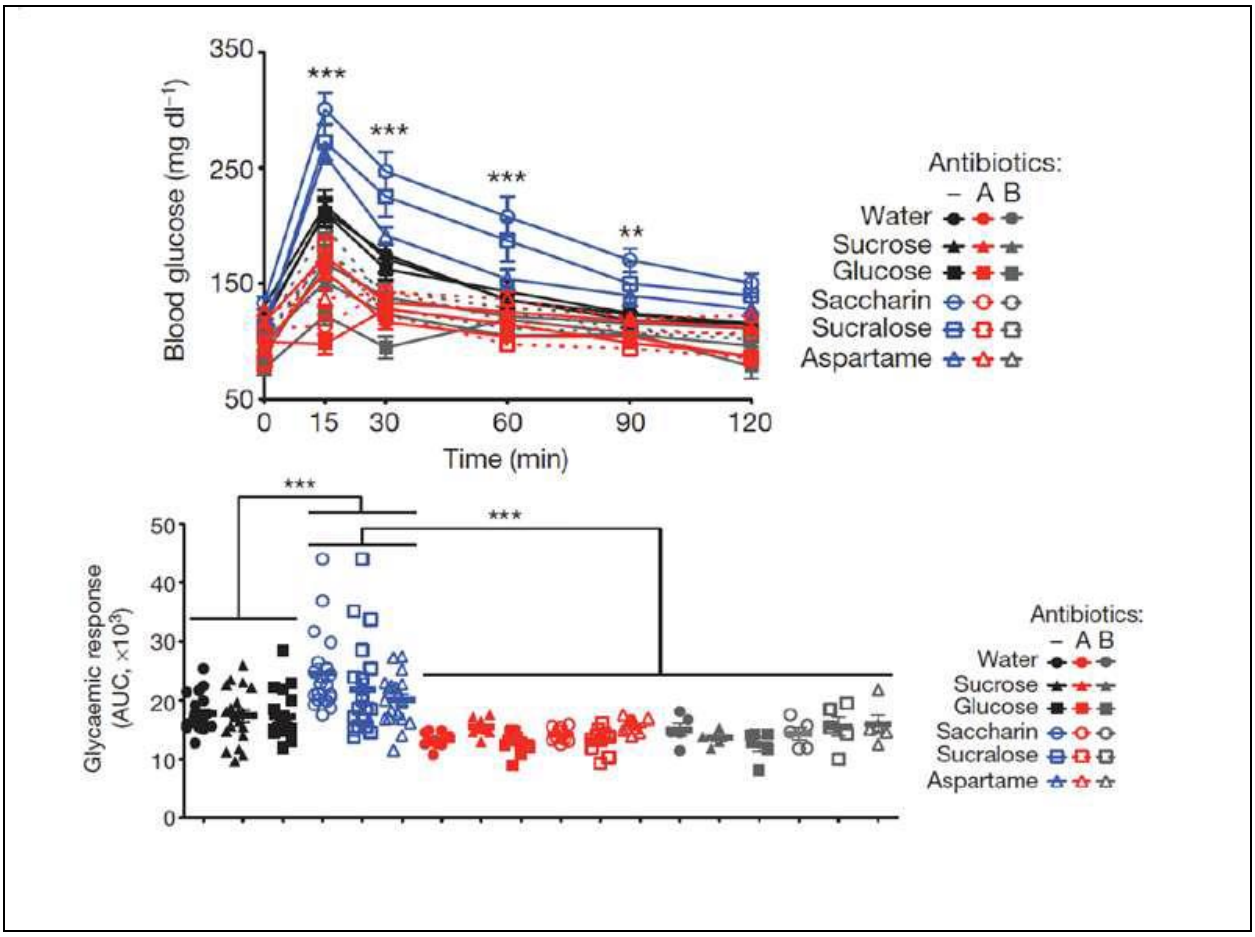
at least 50 parts by weight of a saccharine-type sweetener, at least 0.15 part by weight of glycyrrhizine, neohesperidin dihydrochalcone

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

(Suez et al, 2014)

Nature 514, 181–186




Blood glucose (mg dl⁻¹)
350
250
150
50
0
15
30
60
90
120
Time (min)
***
***
***
**
Antibiotics:
– A B
Water
Sucrose
Glucose
Saccharin
Sucralose
Aspartame
Glycaemic response (AUC, ×10³)
50
40
30
20
10
0
***
***
Antibiotics:
– A B
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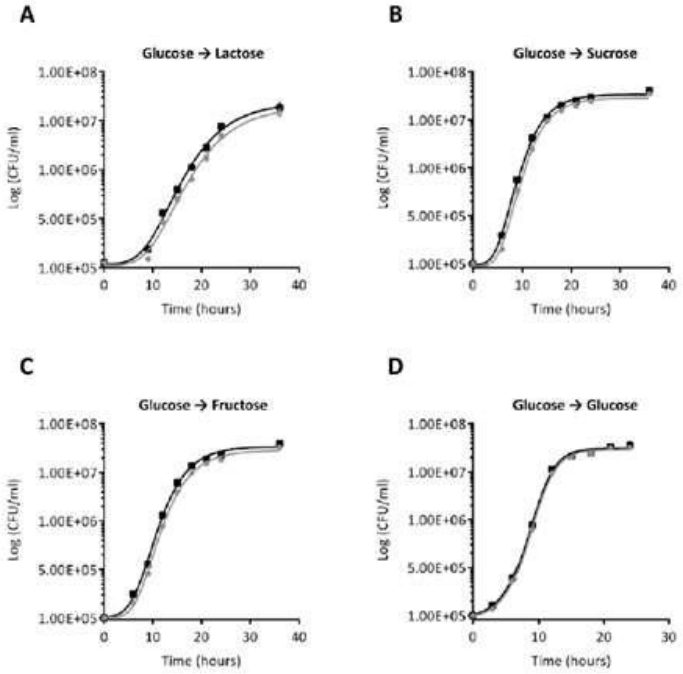


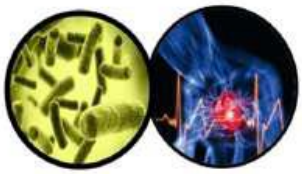
Conclusions

1. Colonic microbiota has undoubtedly a role in the development of metabolic syndrome:
    1. Use of the energy derived from the indigestible portion
    2. Subacute chronic inflammation

- There is not enough evidence that links a specific enterotype with the development of metabolic syndrome. Variability seems to be more important.

- There is evidence that some nutritional treatments (i.e. probiotics) may improve metabolic syndrome.

MICROBIOTA AND CARDIOVASCULAR DISEASES (CVD)



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3. Gut Microbiota and CV
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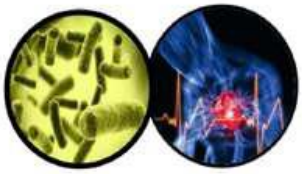
   - Molecular mechanism

4. Prebiotics and/or probiotics as strategies to treat CVD

MICROBIOTA AND CARDIOVASCULAR DISEASES (CVD)



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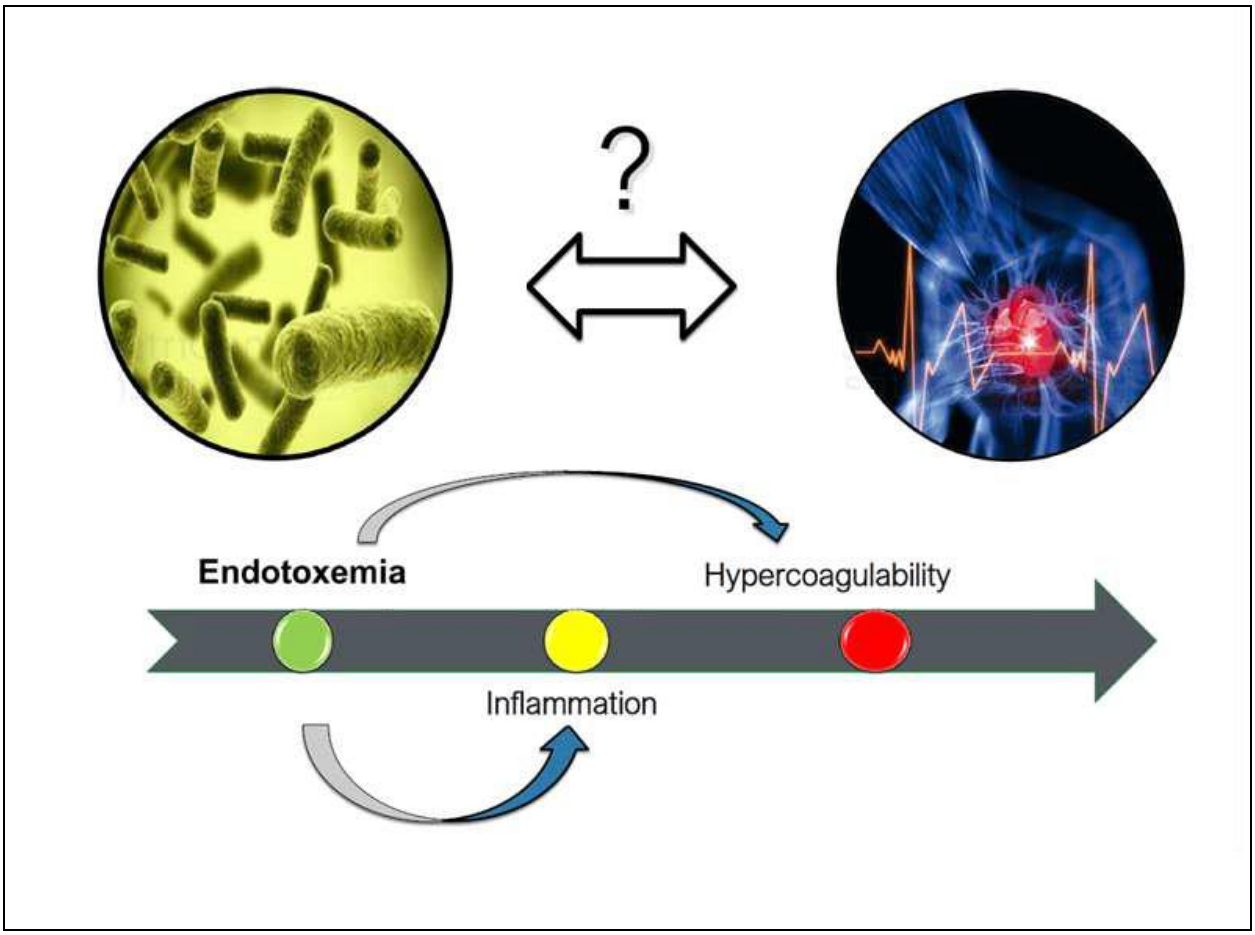
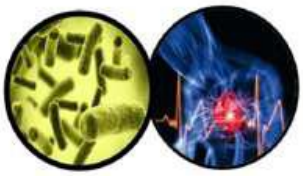

?
Endotoxemia
Hypercoagulability
Inflammation

MICROBIOTA AND CARDIOVASCULAR DISEASES (CVD)



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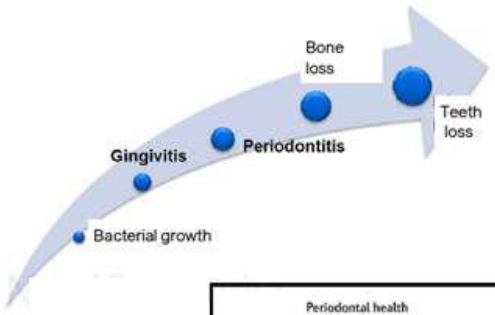
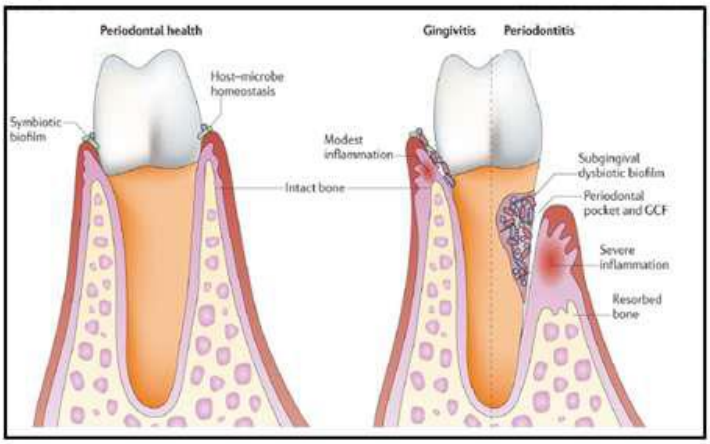
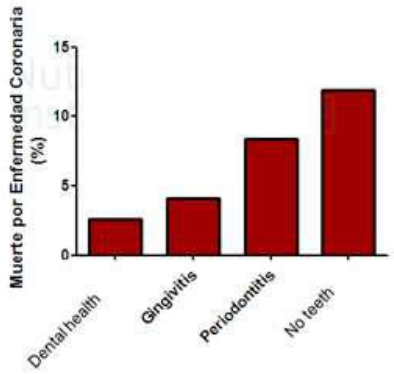


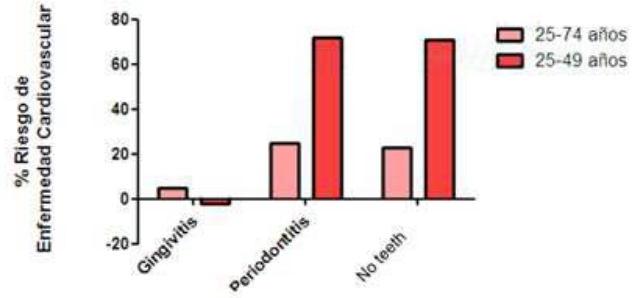
Chronic Inflammation ⇨ Cardiovascular Disease



Hajishengallis et al. Nature Reviews Immunology 2015, 15: 30–44

Dental Disease and Risk of Cardiovascular Disease and Mortality





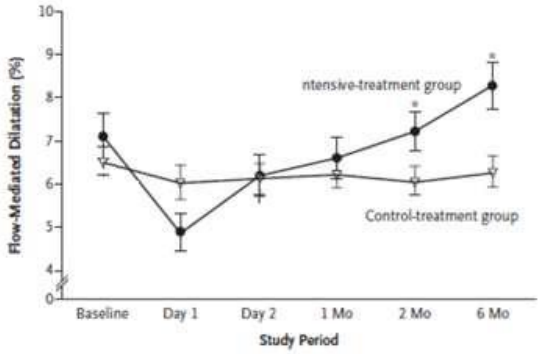
DeStefano et al. BMJ 1993 Mar 13; 306(6879):688-91

Intensive periodontitis treatment improves endothelial function

Table 2. Periodontal Disease at Baseline and 2 Months and 6 Months after Periodontal Therapy.*

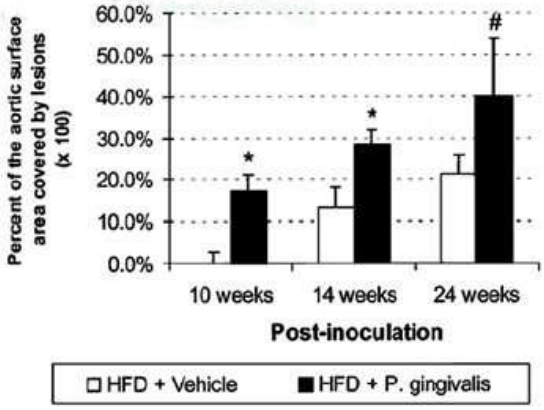
Variable	Control-Treatment Group			Intensive-Treatment Group		
	Baseline	2 Months	6 Months	Baseline	2 Months	6 Months
Total no. of teeth	27±3	27±3	27±3	27±3	25±4†‡	25±4†‡
No. of lesions (periodontal pockets)	84±26	81±27	80±31	82±27	20±15†‡	14±12†‡
Sites with detectable plaque (%)§	63±21	42±22†	47±22†	66±20	15±10†‡	25±18†‡
Sites with gingival bleeding (%)¶	68±17	63±19‖	65±20‖	66±18	24±13†‡	26±16†‡

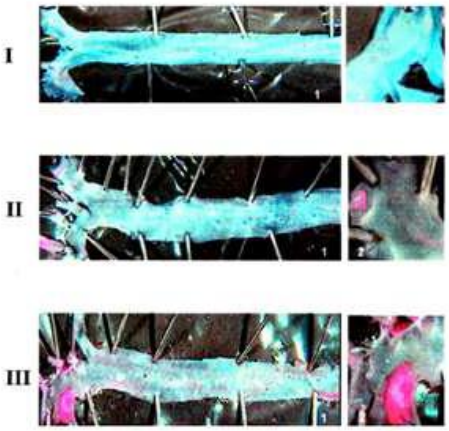
* Plus–minus values are means ±SD.
† P<0.001 for the comparison with baseline.
‡ P<0.001 for the comparison with the standard-treatment group.



Tonetti et al. N Engl J Med 2007; 356:911-920

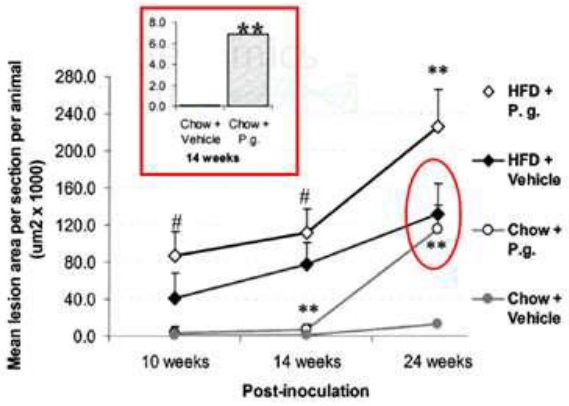
Porphyromonas gingivalis infection speeds up the progression of Aterosclerosis in the murine model ApoE+/-

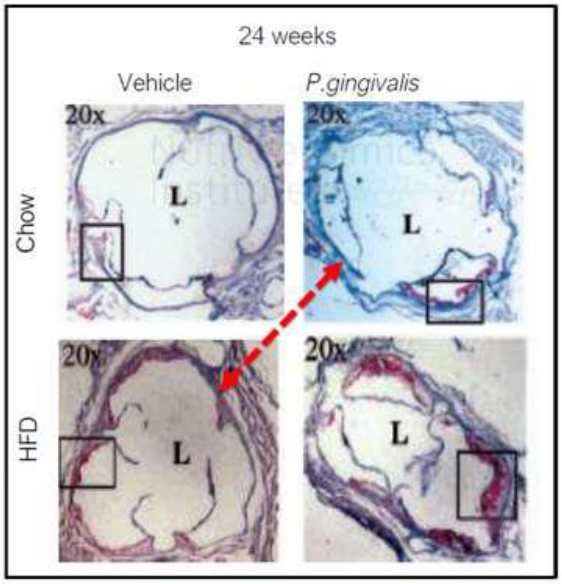




Li et al. Circulation 2002 Feb 19; 105(7):861-7

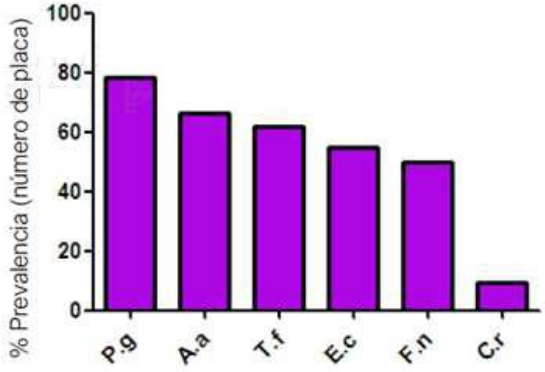
Porphyromonas gingivalis per se causes an aterosclerosis lesion similar to that induced by a high-fat diet





Li et al. Circulation 2002 Feb 19; 105(7):861-7

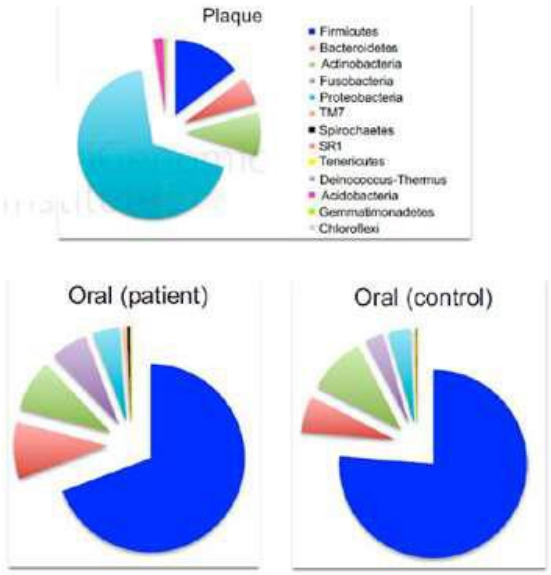
Periodontal bacteria detection in the atheromatous plaque of the carotid artery through Nested polymerase chain reaction (Nested PCR)

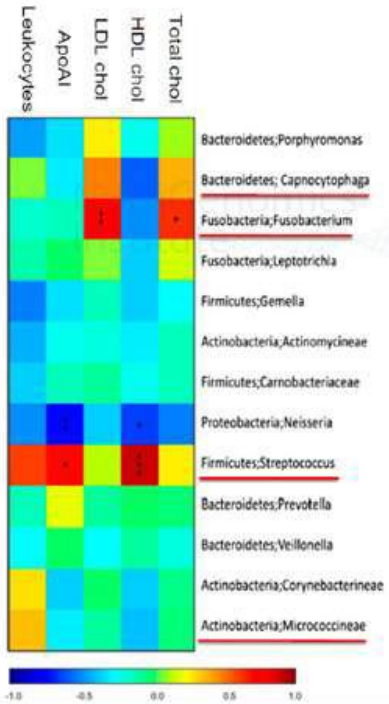


P.g	*Porphyromonas gingivalis*
A.a	*Aggregatibacter actinomycetemcomitans*
T.f	*Tannerella forythia*
E.c	*Ekienella corrodens*
F.n	*Fusobacterium nucleatum*
C.r	*Campylobacter rectus*

Figuero et al. J Periodontol 2011; 82(10):1469-1477

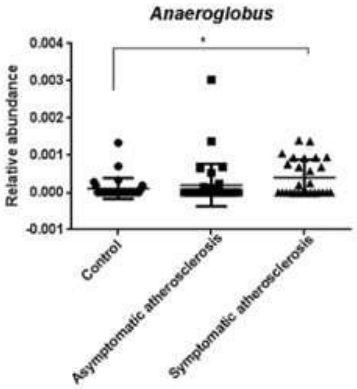
Correlation between bacteria abundance in the oral microbiota and cardiovascular risk factors





Koren et al. PNAS 2011; 108(1): 4592-4598

Differential periodontal microbiota in en symptomatic atherosclerosis patients

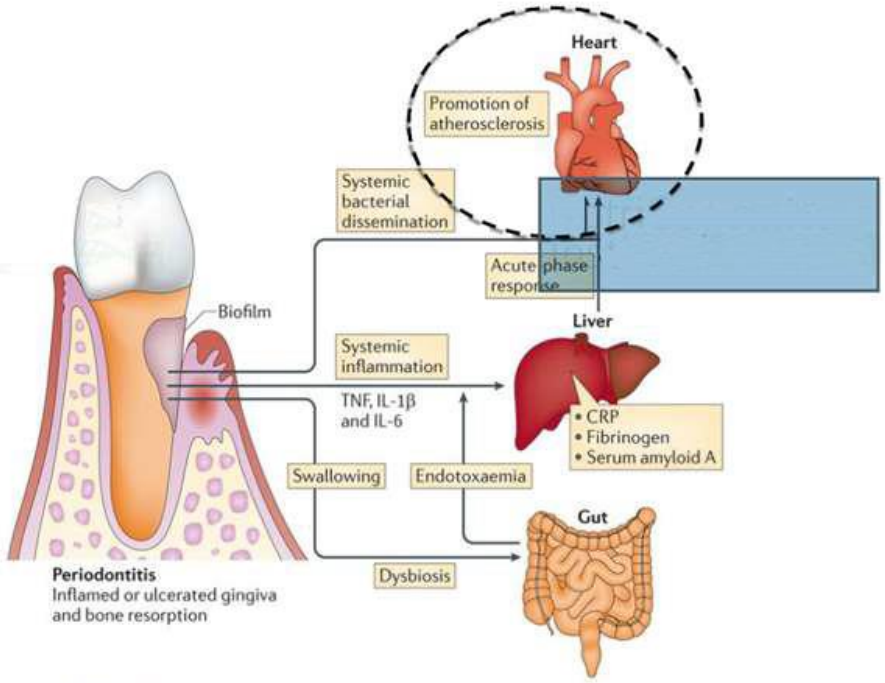


Correlation between oral microbial taxa at genus level and cardiovascular risk factors.

	uCRP	Cholesterol	HDL	LDL	Triglycerides	ApoA1	ApoB
Lactobacillus	N.S	N.S	N.S	N.S	N.S	N.S	$P = 0.038$, $r^2 = 0.06$ +
Capnocytophaga	N.S	$P = 0.016$, $r^2 = 0.08$ −	N.S	$P = 0.036$, $r^2 = 0.068$ −	N.S	N.S	N.S
Catonella	N.S	N.S	$P = 0.020$, $r^2 = 0.083$ +	N.S	N.S	$P = 0.021$, $r^2 = 0.082$ +	N.S
Parvimonas	$P = 0.015$, $r^2 = 0.065$ +	N.S	N.S	N.S	N.S	N.S	N.S

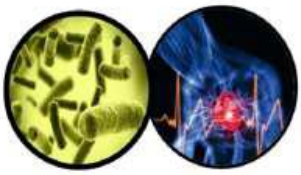
Fak et al. Atherosclerosis 243 (2015): 573-578

MECHANISM: PERIODONTITIS AND CARDIOVASCULAR DISEASE



Hajishengallis et al. Nature Reviews Immunology 2015, 15: 304.

MICROBIOTA AND CARDIOVASCULAR DISEASES (CVD)



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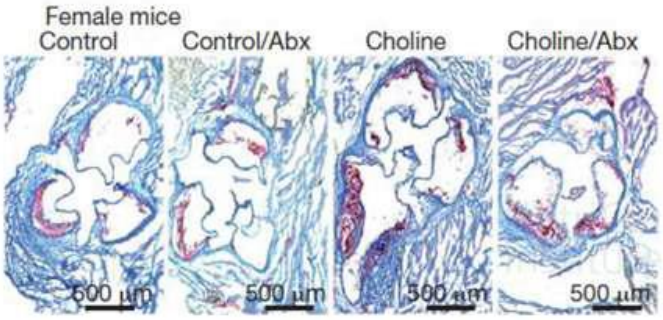
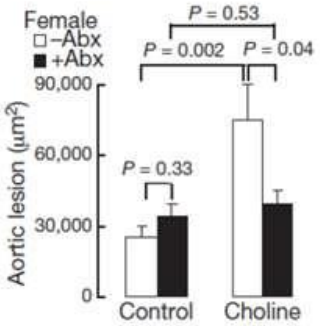
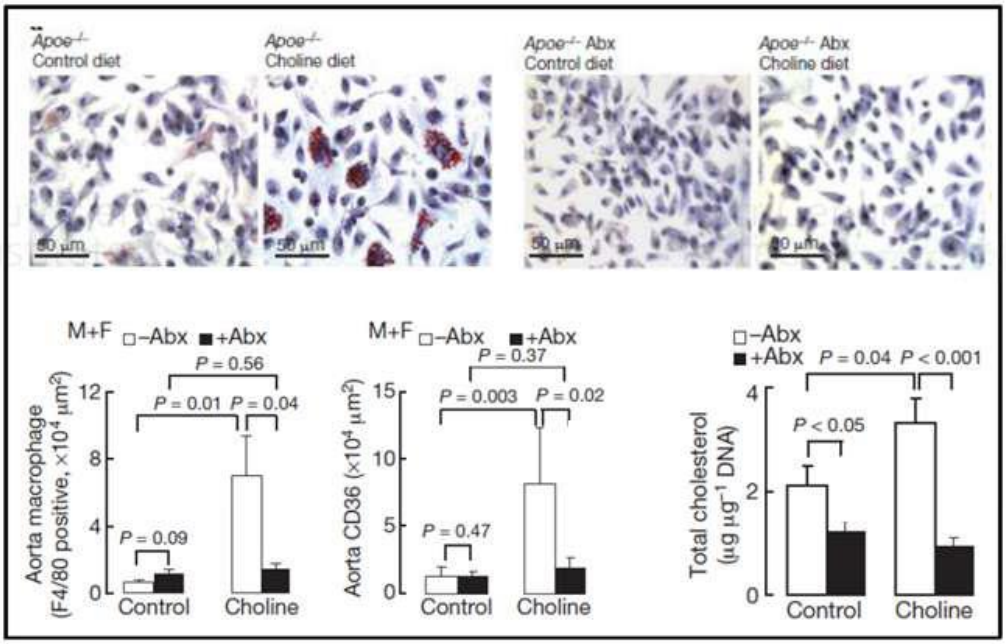
Gut microbiota increases aortic lesion induced by choline





Wang et al. Nature (2011), 472(73411): 57-63

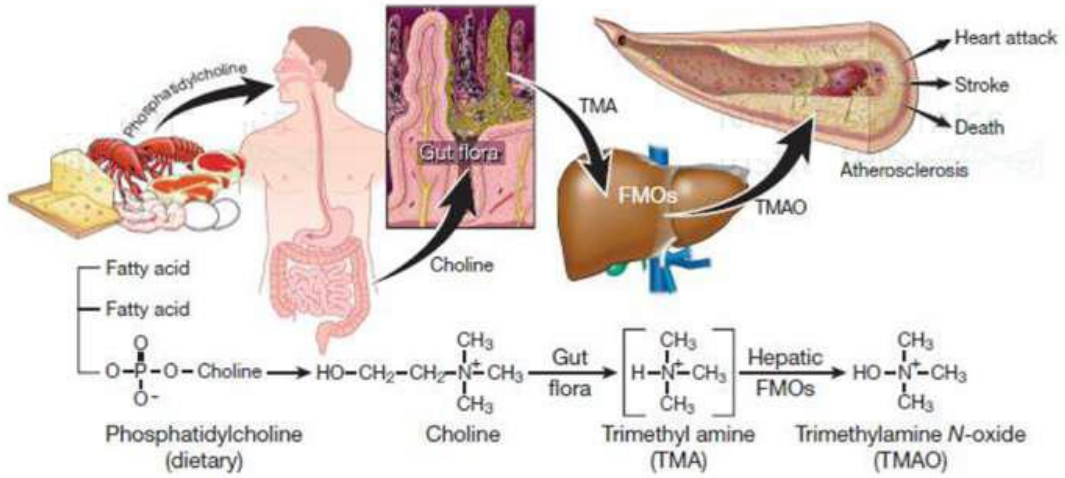
Gut microbiota acts on the homeostasis of plasma cholesterol levels



Wang et al. Nature (2011), 472(73411): 57-63

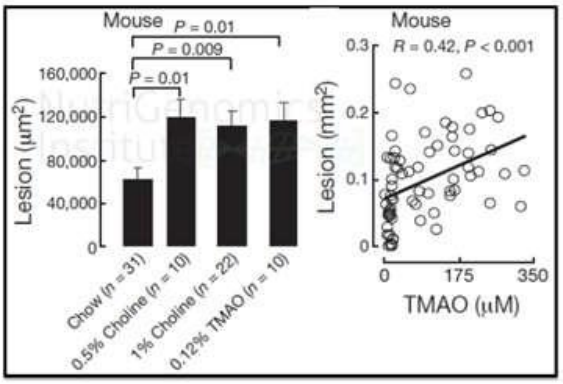
Trimethylamine *N*-oxide (TMAO)

Proaterogenic metabolite dependent on the gut microbiota

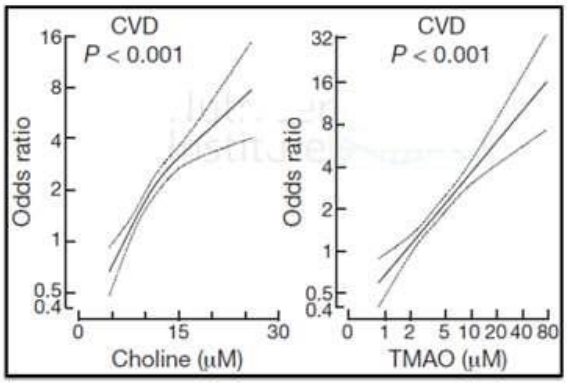


Wang et al. Nature (2011), 472(73411): 57-63

Correlation between TMAO plasma levels and atherosclerotic lesion degree and cardiovascular disease



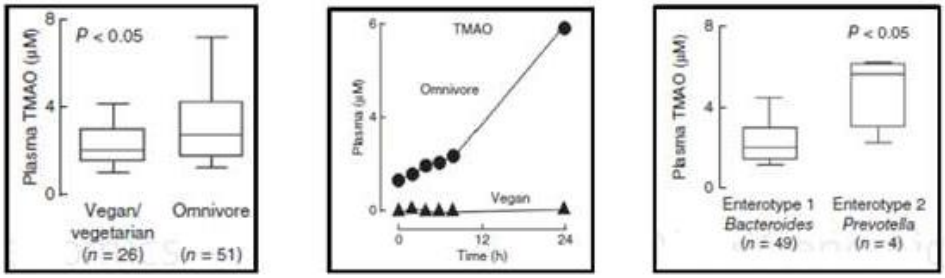
Ratón C57BL/6J Apoe-/-

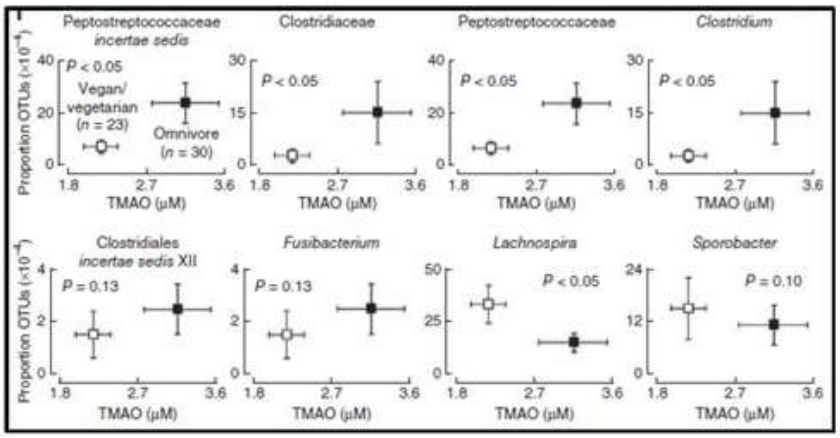


Cohorte (1876 sujetos)

Wang et al. Nature (2011), 472(73411): 57-63

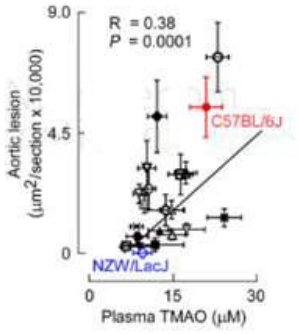
Importance of the microbiota composition in the TMAO metabolism

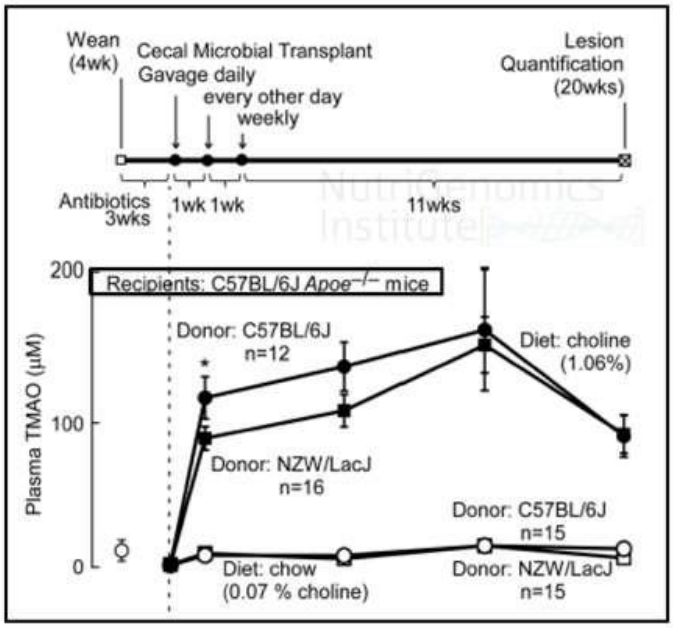




Koeth et al. Nature Medicine 2013, 19(5):576-587

Transmission of Atherosclerosis Susceptibility through Microbial Transplant





Gregory et al. The Journal of Biological Chemistry 2015, 290(9):5647-5660

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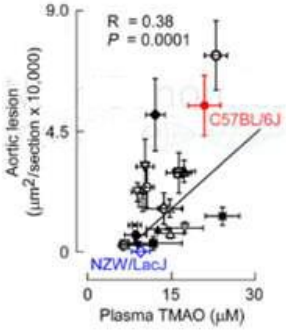

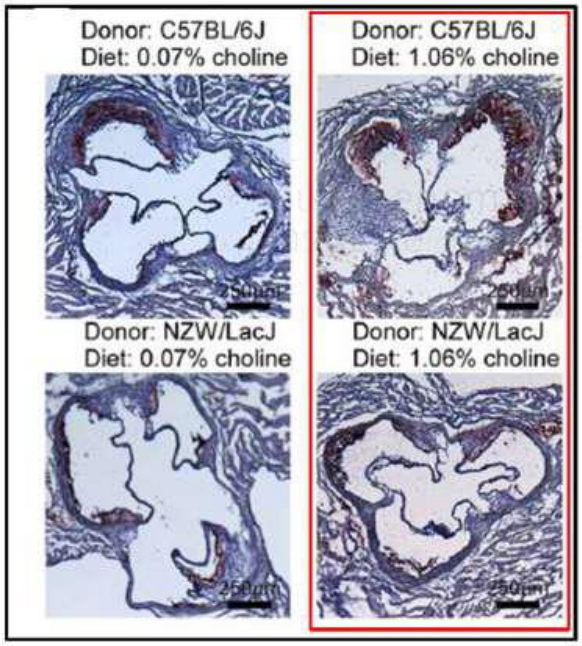

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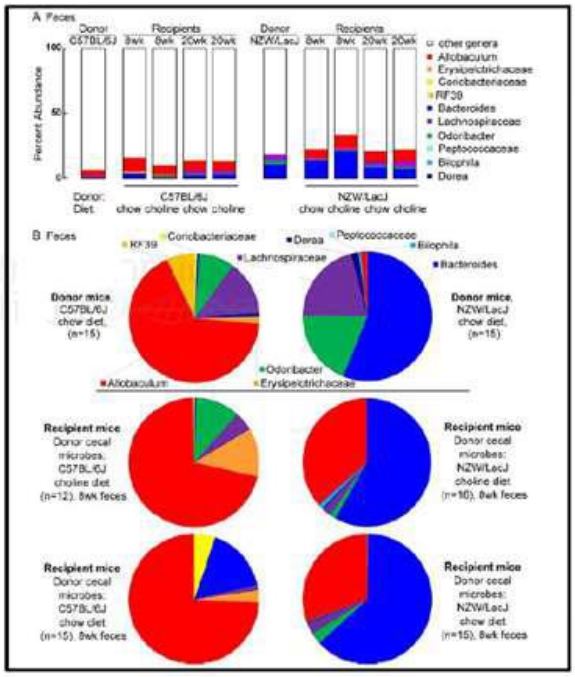
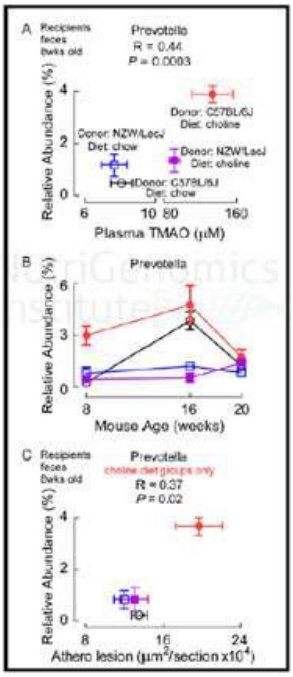
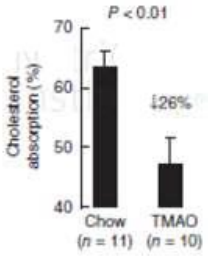


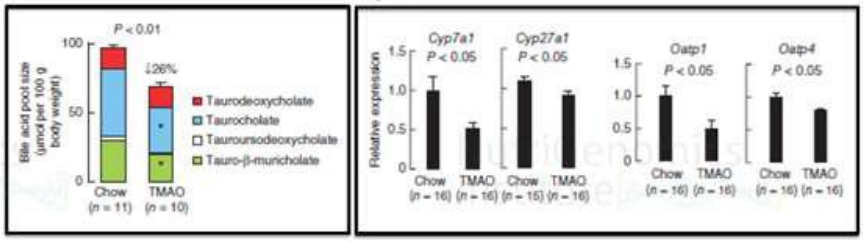


Gregory et al. The Journal of Biological Chemistry 2015, 290(9):5647-5660

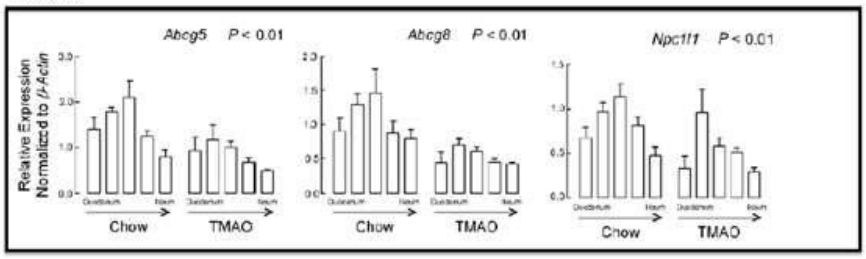
TMAO reduces total cholesterol absorption associated with a reduction in the bile acid pool and an inhibition on cholesterol reverse transport



Higado

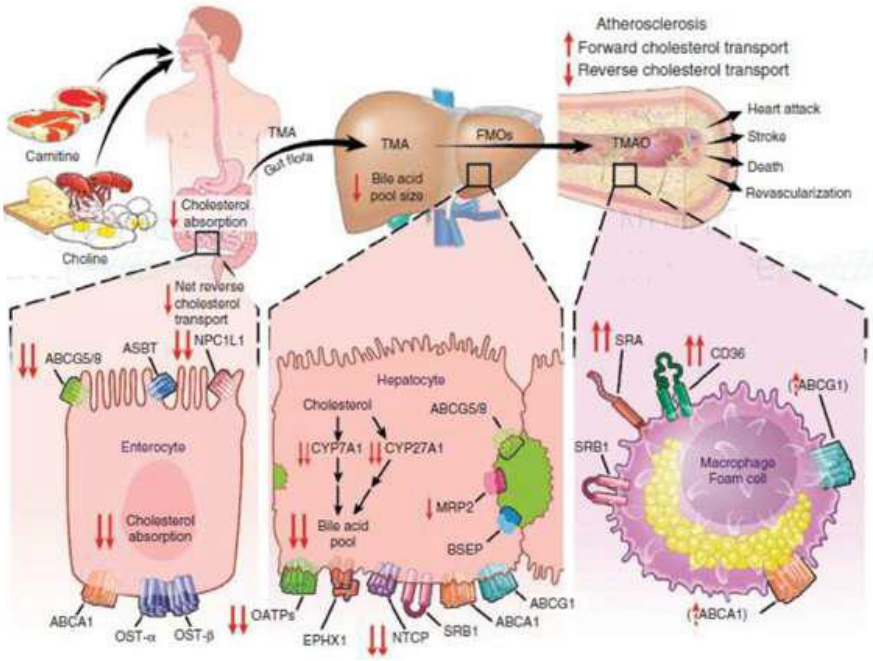


Intestino



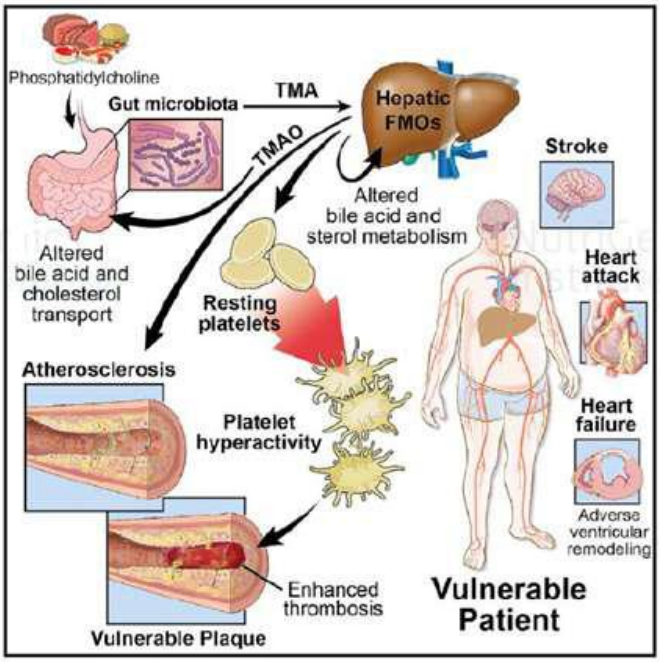
Koeth et al. Nature Medicine 2013, 19(5):576-587

TMAO PRO-ATHEROSCLEROTIC MECHANISM



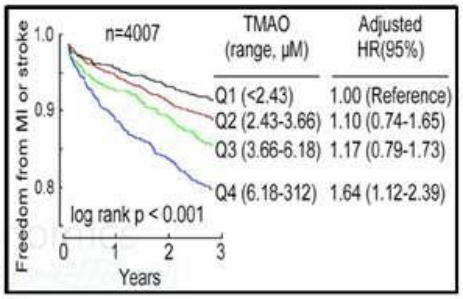
Koeth et al. Nature Medicine 2013, 19(5):576-587

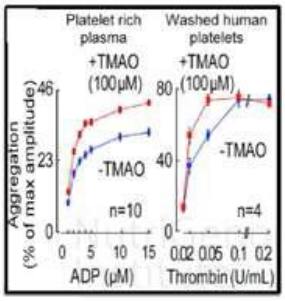
TMAO PRO-TROMBOTIC MECHANISM

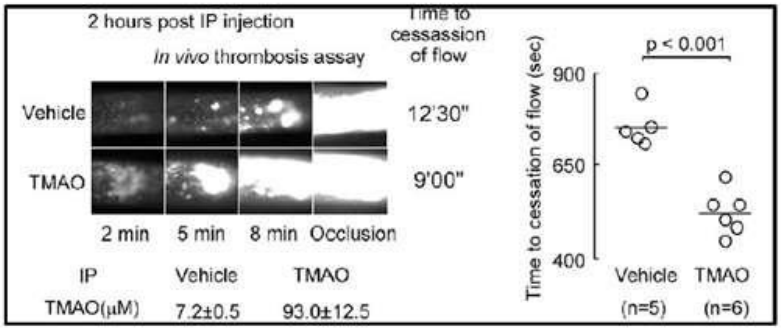


Wolfei et al. Cell 2016, 165:111-124

TMAO increases platelet hyperreactivity and trombosis risk







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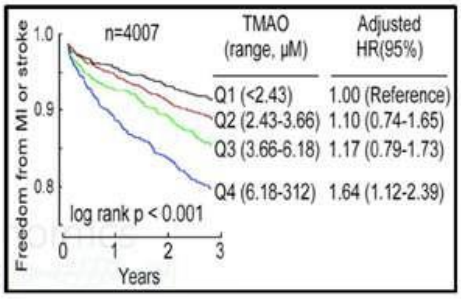

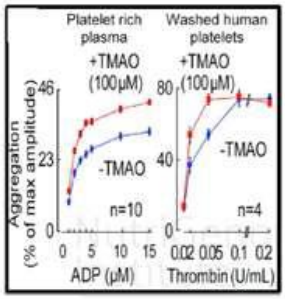

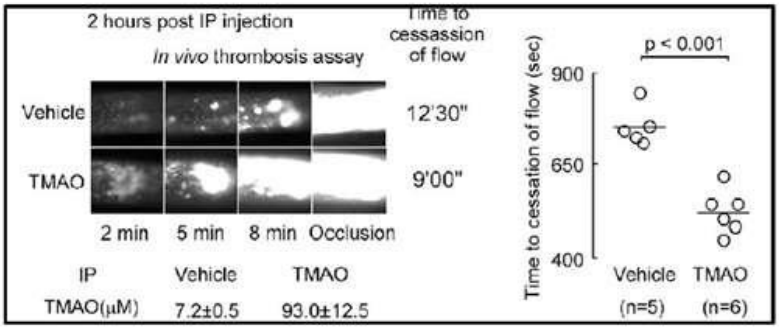

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Probiotics Antimicrob Proteins. 2016 Jun;8(2):61-72. doi: 10.1007/s12602-016-9214-1.

Lactobacillus acidophilus Increases the Anti-apoptotic Micro RNA-21 and Decreases the Pro-inflammatory Micro RNA-155 in the LPS-Treated Human Endothelial Cells.

Kalani M[1,2], Hodjati H[3], Sajedi Khanian M[4], Doroudchi M[5].

Benef Microbes. 2016 Jun;7(3):443-51. doi: 10.3920/BM2015.0146. Epub 2016 Feb 3.

Lactobacillus plantarum CUL66 can impact cholesterol homeostasis in Caco-2 enterocytes.

Michael DR[1], Moss JW[2], Calvente DL[1], Garalova I[1], Plummer SF[1], Ramji DP[2].

Probiotics Antimicrob Proteins. 2011 Dec;3(3-4):194-203. doi: 10.1007/s12602-011-9086-3.

Lactobacillus rhamnosus BFE 5264 and Lactobacillus plantarum NR74 Promote Cholesterol Excretion Through the Up-Regulation of ABCG5/8 in Caco-2 Cells.

Yoon HS[1], Ju JH[2], Kim H[1], Lee J[1], Park HJ[1], Ji Y[1], Shin HK[1], Do MS[1], Lee JM[3], Holzapfel W[4].

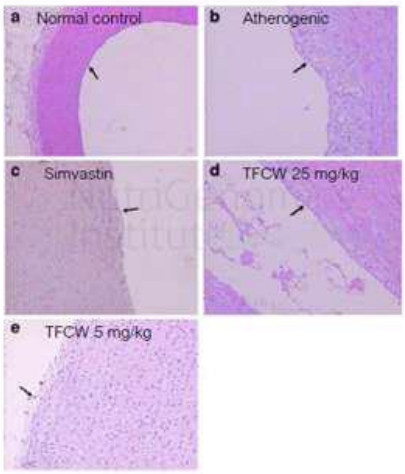
Anti-atherosclerotic effect of fermented traditional cheese whey on atherosclerotic rabbits and identification of probiotics

Group	TC	TG	HDL-C	LDL-C
Normal control	4.75 ± 2.00	0.53 ± 0.16	1.03 ± 0.22	0.18 ± 0.03
Atherogenic group	22.79 ± 2.13*	3.20 ± 1.32*	2.20 ± 0.95*	15.85 ± 3.2*
Simvastatin (20 mg/kg)	17.55 ± 1.6**	0.86 ± 0.22**	2.55 ± 0.23*	7.23 ± 2.87**
TFCW (25 mg/kg)	16.74 ± 3.4**	1.49 ± 0.73**	2.16 ± 0.69*	5.52 ± 1.76**
TFCW (50 mg/kg)	15.20 ± 5.25**	0.50 ± 0.20**	2.33 ± 0.18*	6.7 ± 2.28**

* $P < 0.05$ vs. Normal control

Group	CRP (mg/L)	Body weight (kg)	ICAM-1 (μg/L)	VCAM-1 (μg/L)
Normal control	0.98 ± 0.03	3.21 ± 0.37	32.89 ± 16.00	16.90 ± 6.03
Atherogenic group	15.03 ± 9.12*	3.03 ± 0.63	118.50 ± 30.12*	51.23 ± 9.00*
Simvastatin (20 mg/kg)	3.43 ± 0.80**	2.90 ± 0.15	63.65 ± 28.98**	41.14 ± 7.81**
TFCW (25 mg/kg)	3.33 ± 0.50**	2.35 ± 0.30	75.60 ± 28.40**	41.12 ± 8.90**
TFCW (50 mg/kg)	1.34 ± 0.90**	3.03 ± 0.30	42.25 ± 17.80**	41.75 ± 12.32**

* $P < 0.05$ vs. Normal control



Bacteria producing lactic acid
- *Lactobacillus brevis*
- *L. kefiranofacions*
- *L. helveticus*
- *L. Casei*
- *L. plantarum*
- *L. kefiri*
- *L. lactic*

Yeasts
Saccharomyces unisporus
- *Issatchonkia orientalis*

Nabi et al. BMC Complement Altern Med 2016, 16(1):309

Probiotic Soy Product Supplemented with Isoflavones Improves the Lipid Profile of Moderately Hypercholesterolemic Men: A Randomized Controlled Trial

Enterococcus faecium CRL183

Lactobacillus helveticus 416

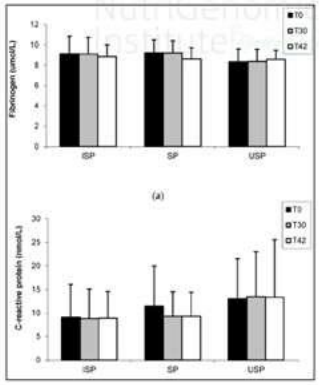
Serum lipids levels during the experiment

Time	ISP ($n = 17$)	SP ($n = 17$)	USP ($n = 15$)
TC (mmol/L)			
T0	$5.47 \pm 0.59^{a,A}$	$5.76 \pm 1.02^{a,A}$	$5.60 \pm 0.76^{a,A}$
T30	$4.65 \pm 0.48^{b,B}$	$5.44 \pm 0.93^{a,A}$	$5.52 \pm 0.76^{a,A}$
T42	$4.72 \pm 0.45^{b,B}$	$5.41 \pm 0.86^{a,A}$	$5.50 \pm 0.78^{a,A}$
HDL-C (mmol/L)			
T0	$1.39 \pm 0.22^{a,A}$	$1.38 \pm 0.25^{a,A}$	$1.50 \pm 0.28^{a,A}$
T30	$1.18 \pm 0.23^{a,A}$	$1.33 \pm 0.16^{a,A}$	$1.24 \pm 0.38^{a,A,B}$
T42	$1.21 \pm 0.22^{a,A}$	$1.28 \pm 0.18^{a,A}$	$1.13 \pm 0.38^{a,B}$
LDL-C (mmol/L)			
T0	$3.28 \pm 0.61^{a,A}$	$3.54 \pm 0.92^{a,A}$	$3.14 \pm 0.95^{a,A}$
T30	$2.75 \pm 0.51^{a,A}$	$3.35 \pm 0.84^{a,A}$	$3.41 \pm 0.69^{a,A}$
T42	$2.79 \pm 0.50^{b,A}$	$3.35 \pm 0.86^{ab,A}$	$3.51 \pm 0.63^{a,A}$
TG (mmol/L)			
T0	$1.91 \pm 0.98^{a,A}$	$1.88 \pm 0.88^{a,A}$	$1.97 \pm 1.32^{a,A}$
T30	$1.57 \pm 0.74^{a,A}$	$1.83 \pm 0.89^{a,A}$	$2.18 \pm 1.61^{a,A}$
T42	$1.55 \pm 0.70^{a,A}$	$1.86 \pm 0.93^{a,A}$	$2.15 \pm 1.64^{a,A}$
aHDL-C (mmol/L)			
T0	$4.11 \pm 0.65^{a,A}$	$4.38 \pm 1.12^{a,A}$	$4.08 \pm 0.82^{a,A}$
T30	$3.47 \pm 0.48^{a,B}$	$4.11 \pm 0.98^{a,A}$	$4.28 \pm 0.99^{a,A}$
T42	$3.50 \pm 0.46^{b,B}$	$4.14 \pm 0.92^{ab,A}$	$4.37 \pm 0.96^{a,A}$
TC/HDL-C			
T0	$4.11 \pm 0.78^{a,A}$	$4.28 \pm 0.90^{a,A}$	$3.80 \pm 0.83^{a,A}$
T30	$4.07 \pm 0.75^{a,A}$	$4.18 \pm 0.90^{a,A}$	$4.92 \pm 1.69^{a,A}$
T42	$4.00 \pm 0.71^{a,A}$	$4.22 \pm 0.83^{ab,A}$	$5.47 \pm 1.98^{a,A}$

ISP soy probiotic supplemented with isoflavones

SP: soy probiotic

USP: non-fermented soy probioti



Cavallini et al. Nutrients. 2016, 8:52

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HDL-C (mmol/L)			
T0	$1.36 \pm 0.22^{a,A}$	$1.38 \pm 0.25^{a,A}$	$1.50 \pm 0.28^{a,A}$
T30	$1.18 \pm 0.23^{a,A}$	$1.33 \pm 0.16^{a,A}$	$1.24 \pm 0.38^{a,A,B}$
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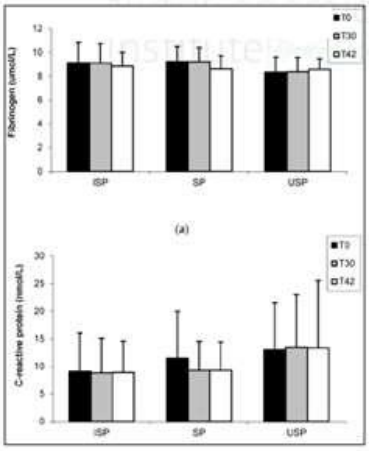
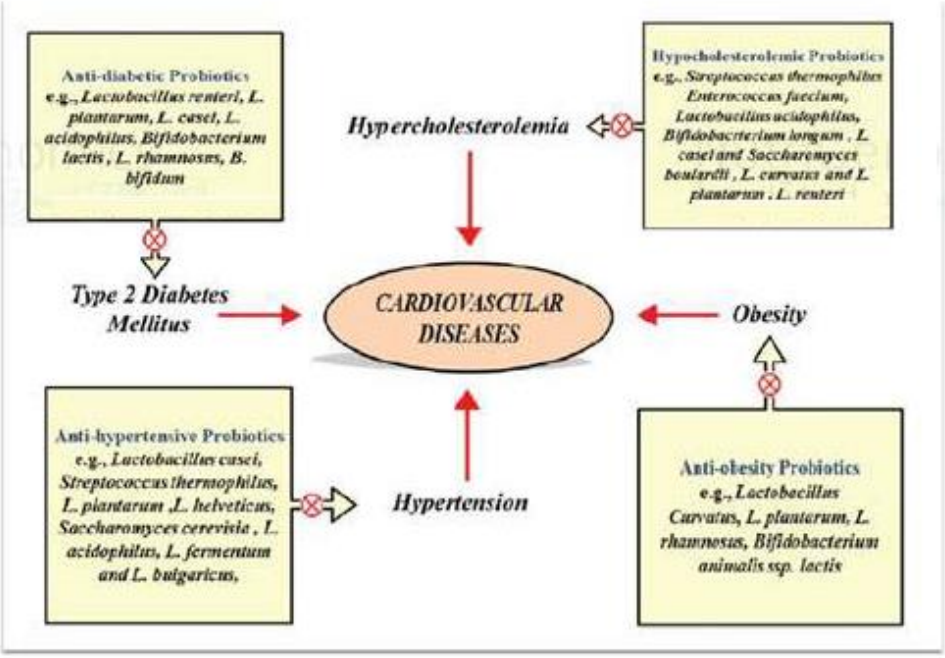


Cavallini et al. Nutrients. 2016, 8:52

Cardiovascular benefits of probiotics: a review of experimental and clinical studies

Ram Mohan Thushara, Surendiran Gangadaran, Zahra Solati and Mohammed H. Moghadasian*



Tushara et al. Food and Function, 2016, 7:632

CONCLUSIONS AND COMMENTS

1. **Microbiota plays an important role in the susceptibility and development of CVD.**

   - Oral infections, such as periodontitis, are related with a greater progression of the atherogenic damage in susceptible individuals.
   - The composition of gut microbiota is a most relevant factor in the development of diet-induced CVD.
   - Some association studies demonstrate that the presence of certain microorganisms in the oral microbiota or the gut microbiota can predict the risk of developing CVD.
   - An adequate periodontal treatment in susceptible individuals, as well as the modulation of gut microbiota by means of prebiotics and/or probiotics may be a suitable strategy to decrease CDV risk.

2. **The studies carried out to date are scarce, and many of them have been carried out on animal models. Therefore, a greater amount of data is needed in order to be able to make these observations general before offering therapeutic strategies based on the modulation of microbiota.**

MICROBIOTA AND NERVOUS SYSTEM DISEASES

1. Introduction
2. "Microbiota-gut-brain" axis: role of the microbiota in the development and physiology of the nervous system
   - "Microbiota-gut-brain" axis
   - Signalling pathways
   - Concept of leaky gut and role in neurological disorders
   - Study models: importance of axenic mice for the understanding of the molecular mechanisms associated
   - Temporal nervous system "windows of vulnerability" to the action of microbiota
   - Importance of maternal microbiota during pre-natal period and early post-natal life
3. Microbiota and Neurodevelopmental Disorders
   - Autism spectrum disorder
4. Microbiota and Mental Disorders
   - Schizophrenia
   - Depression
5. Microbiota and Neurodegenerative Disorders
   - Chronic inflammation associated to aging and instability of the microbiota
   - Alzheimer's Disease (AD)
   - Parkinson's Disease (PD)
   - Amyotrophic Lateral Sclerosis (ALS)
   - Multiple Sclerosis (MS)
6. Gut microbiota modulation as a therapeutic strategy in Nervous System Diseases: use of prebiotics and/or probiotics

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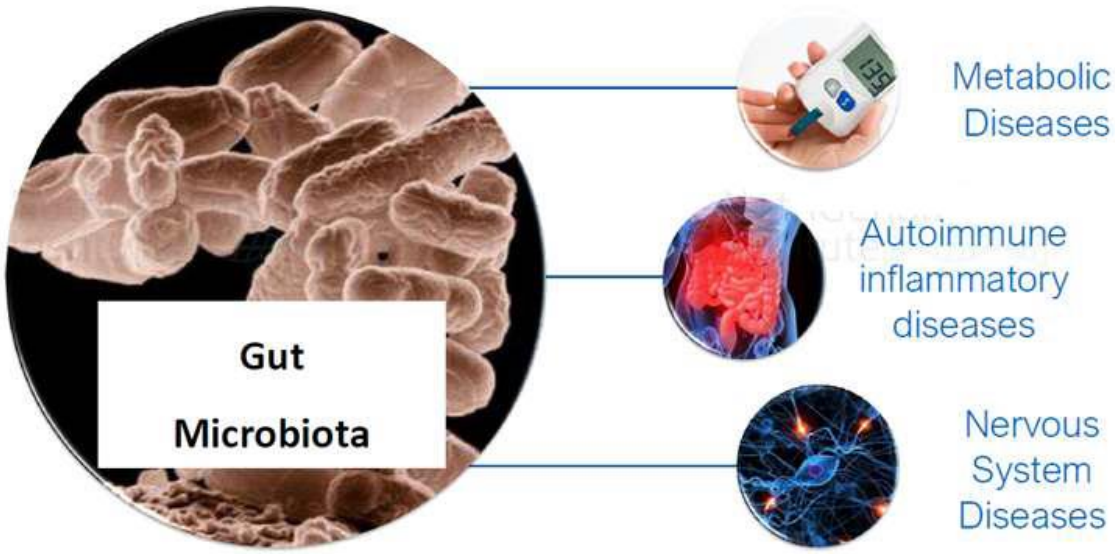
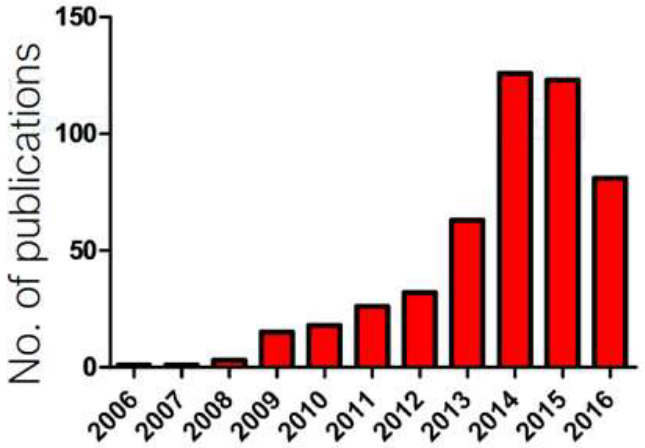

Gut
Microbiota
Metabolic Diseases
Autoimmune inflammatory diseases
Nervous System Diseases

Pubmed search for "microbiota and nervous system"



MENTAL DISORDERS
A SIDE EFECT OF ANTIBIOTICS

- Maniacal disorder
- Stress
- Depression
- Hallucination
- Dementia
- Anxiety
- Schizophrenia
- Delusion

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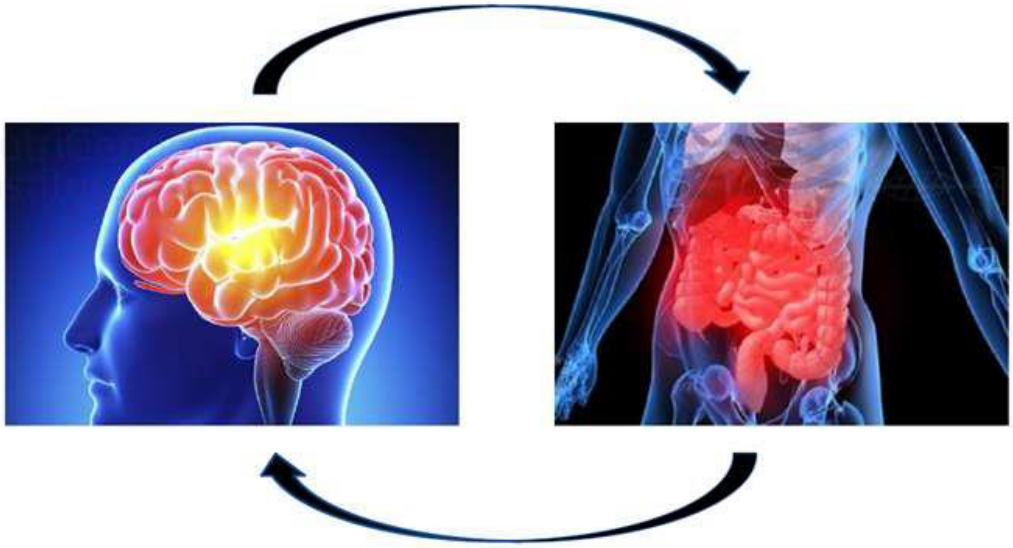
GASTROINTESTINAL AND MENTAL DISORDERS CO-MORBILITY

IS THERE A BIDIRECTIONAL COMMUNICATION SYSTEM?



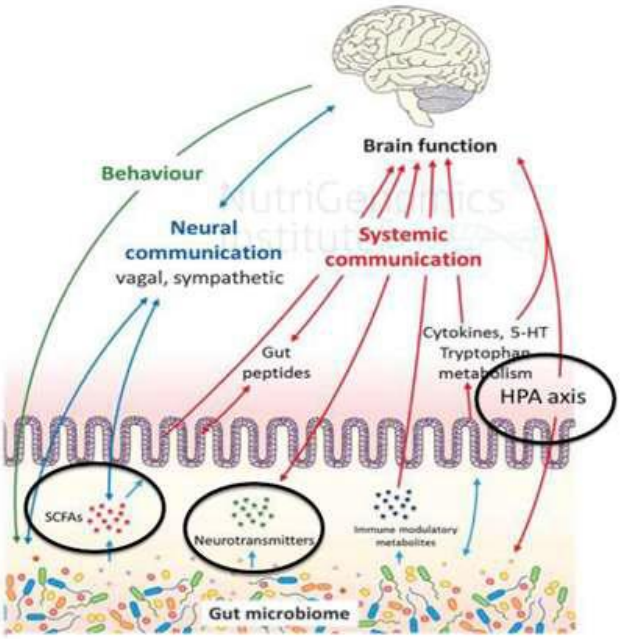
"MICROBIOTA-GUT-BRAIN" AXIS: ROLE OF THE MICROBIOTA IN THE DEVELOPMENT AND PHYSIOLOGY OF THE NERVOUS SYSTEM

"Complex bidirectional communication network which incorporates and links microbiota and intestinal tract signals with cognitive and emotional brain centers through the involvement of the central nervous system, the autonomic nervous system (sympathetic and parasympathetic), the enteric nervous system, the neuroendocrine system and the neuroimmune system".

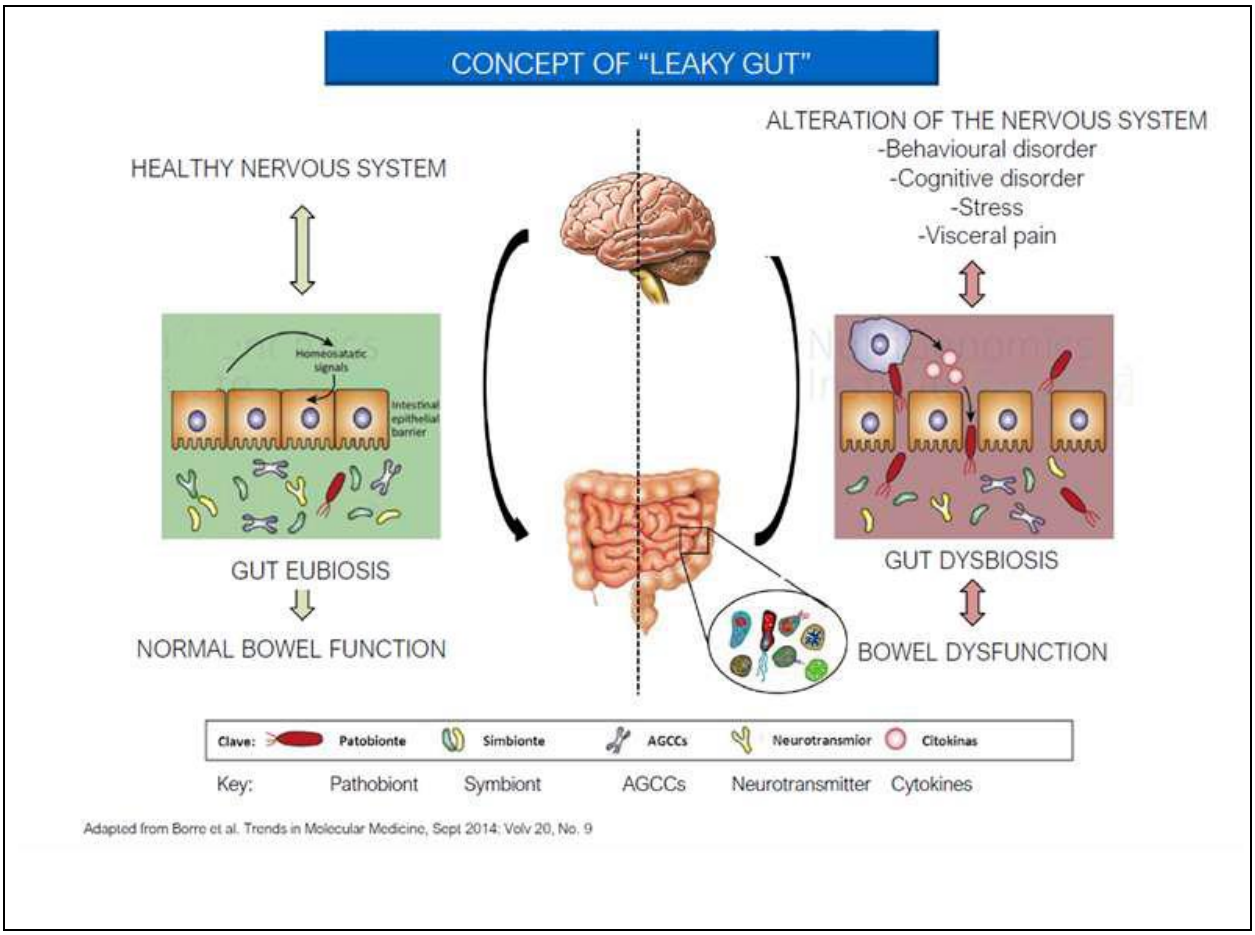
"MICROBIOTA-GUT-BRAIN" AXIS

Signalling PATHWAYS OF THE "MICROBIOTA-GUT-BRAIN" AXIS

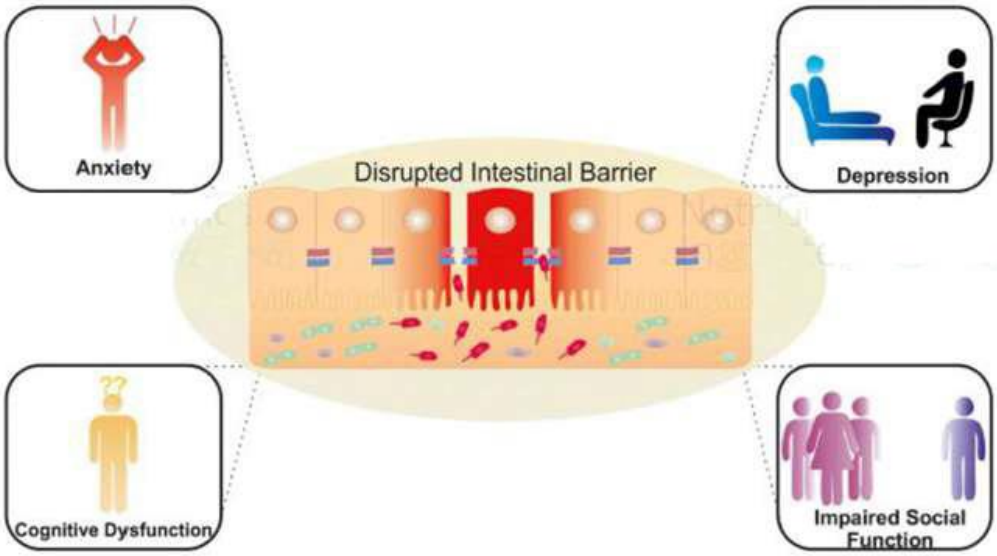
- Microbial metabolites
  - Short-chain fatty acids (SCFAs)
  - Neurotransmitters (GABA, serotonine)
- Neural Pathway: vagus nerve and enteric system
- Inmune Pathway (cytokines)
- Endocrine Pathway (cortisol)
- Tryptophan Metabolism



Rogers et al. Molecular Psychiatry, 2016: Vol 21, 738-748



Adapted from Borre et al. Trends in Molecular Medicine, Sept 2014; Volv 20, No. 9



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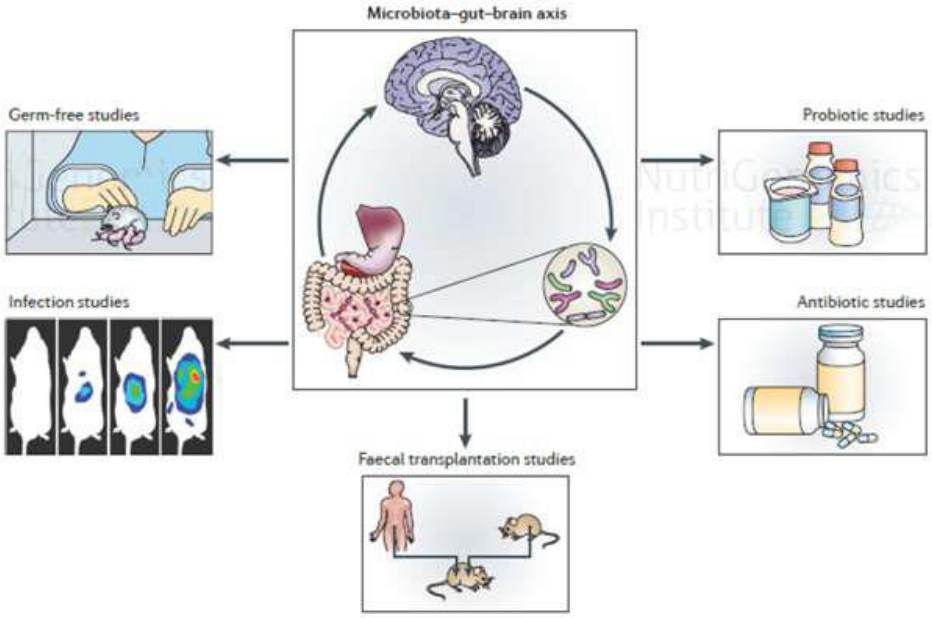
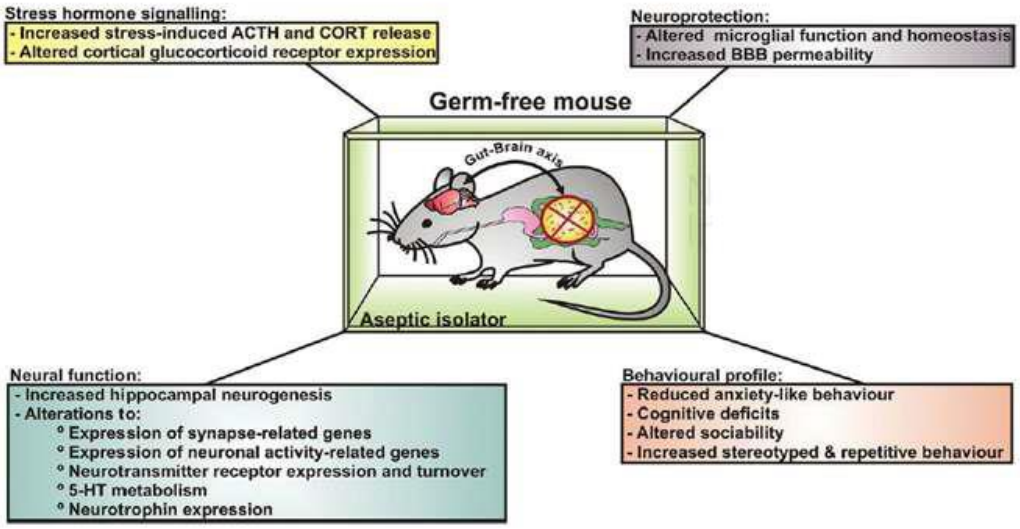
STUDY MODELS ON THE ROLE OF MICROBIOTA IN THE DEVELOPMENT AND MODULATION OF THE NERVOS SYSTEM

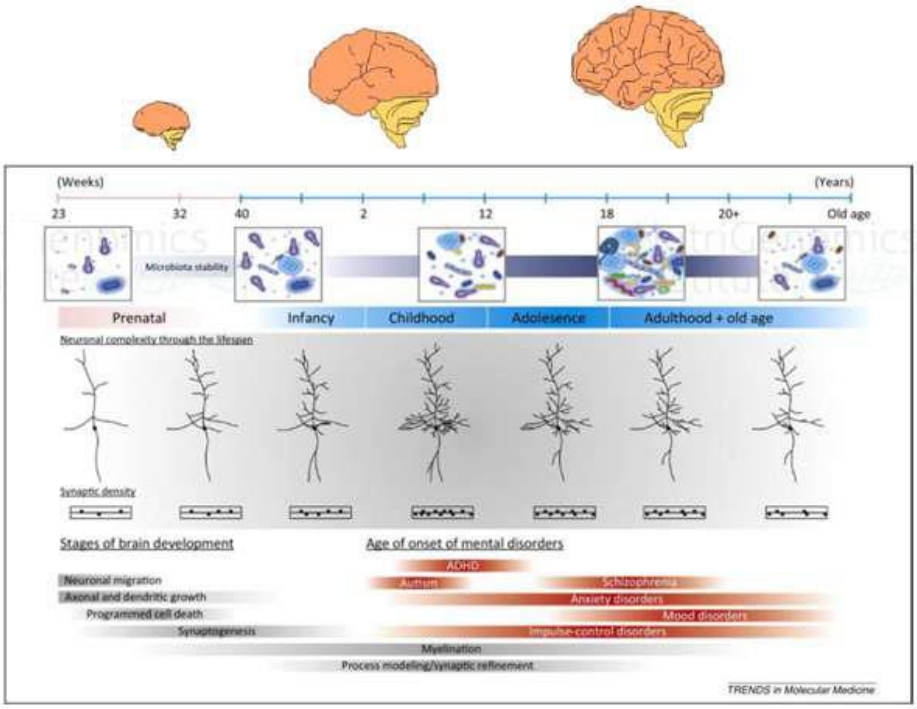


Cryan and Dian, Nature Reviews 2012, 13:701-712



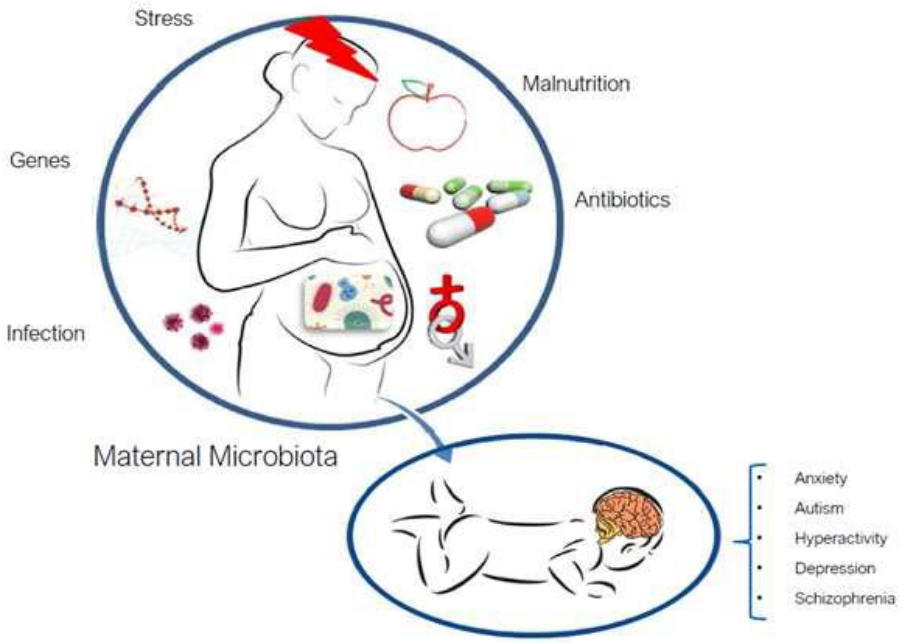
Pauline Luczynski et al. Int J Neuropsychopharmacology 2016, 19:pyw020

MICROBIOTA: DEVELOPMENT AND PHYSIOLOGY OF THE NERVOUS SYSTEM



Adaptado de Borre et al. Trends in Molecular Medicine, Sept 2014: Vol 20, No. 9

MATERNAL MICROBIOTA, KEY ELEMENT DURING PRE-NATAL PERIOD



Adaptado de O'Mahoni et al. Neuroscience 2015, doi.org/10.1016/j.neuroscience.2015.09.068

Effects of prenatal maternal stress on serotonin and fetal development

Joey St-Pierre [a,1], Laetitia Laurent [a,1], Suzanne King [b], Cathy Vaillancourt [a,*]

J Neurosci. 2010 Mar 10;30(10):3826-30. doi: 10.1523/JNEUROSCI.5560-09.2010.

Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behavior in nonhuman primate offspring.

Sullivan EL[1], Grayson B, Takahashi D, Robertson N, Maier A, Bethea CL, Smith MS, Coleman K, Grove KL.

Behav Brain Res. 2013 Feb 1;238:193-9. doi: 10.1016/j.bbr.2012.10.028. Epub 2012 Oct 22.

Maternal diet rich in omega-6 polyunsaturated fatty acids during gestation and lactation produces autistic-like sociability deficits in adult offspring.

Jones KL[1], Will MJ, Hecht PM, Parker CL, Beversdorf DQ.

Horm Behav. 2015 Nov;76:153-61. doi: 10.1016/j.yhbeh.2015.04.008. Epub 2015 Apr 24.

Maternal high-fat diet programming of the neuroendocrine system and behavior.

Sullivan EL[1], Riper KM[2], Lockard R[2], Valleau JC[3].

J Autism Dev Disord. 2010 Dec;40(12):1423-30. doi: 10.1007/s10803-010-1006-y.

Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders.

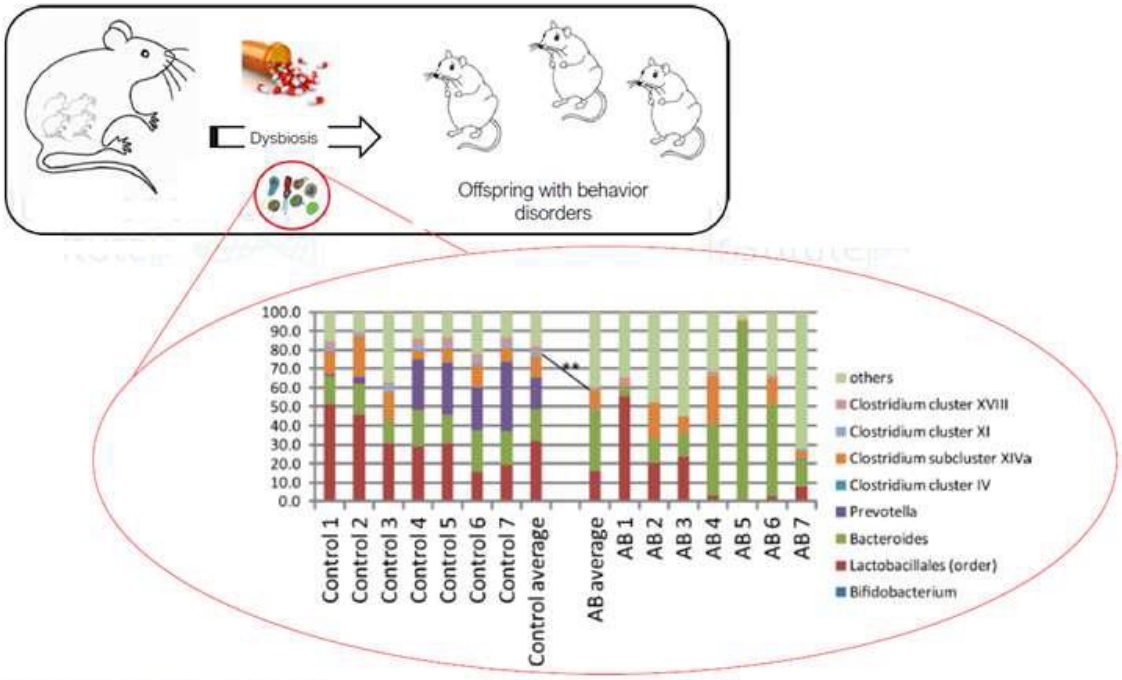
Atladottir HO[1], Thorsen P, Østergaard L, Schendel DE, Lemcke S, Abdallah M, Parner ET.

Prog Neuropsychopharmacol Biol Psychiatry. 2016 Jun 21;71:76-82. doi: 10.1016/j.pnpbp.2016.06.010. [Epub ahead of print]

Maternal gut and fetal brain connection: Increased anxiety and reduced social interactions in Wistar rat offspring following peri-conceptional antibiotic exposure.

Degroote S[1], Hunting DJ[2], Baccarelli AA[3], Takser L[4].

Behavioural disorders associated to changes in the maternal microbiota induced by the administration non-absorbable antibiotics during the gestation period



Tochitani et al. PLoS One 2016: 11(1):e0138293

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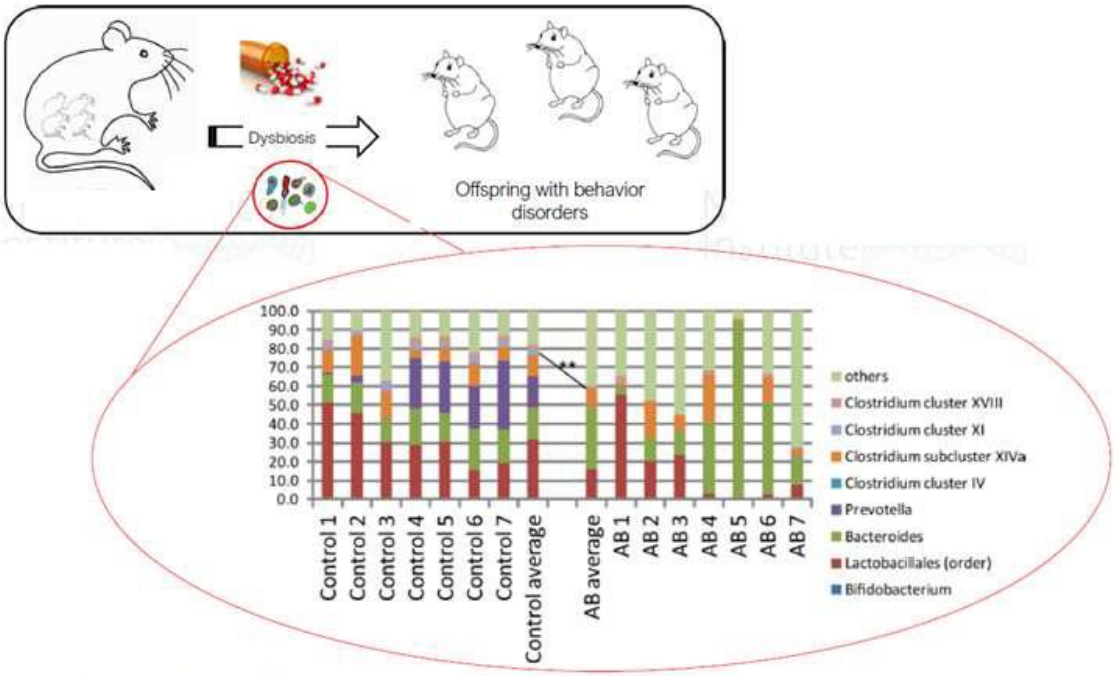

Tochitani et al. PLoS One 2016: 11(1):e0138293

MICROBIOTA AND NERVOUS SYSTEM DISEASES

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   - Parkinson's Disease (PD)
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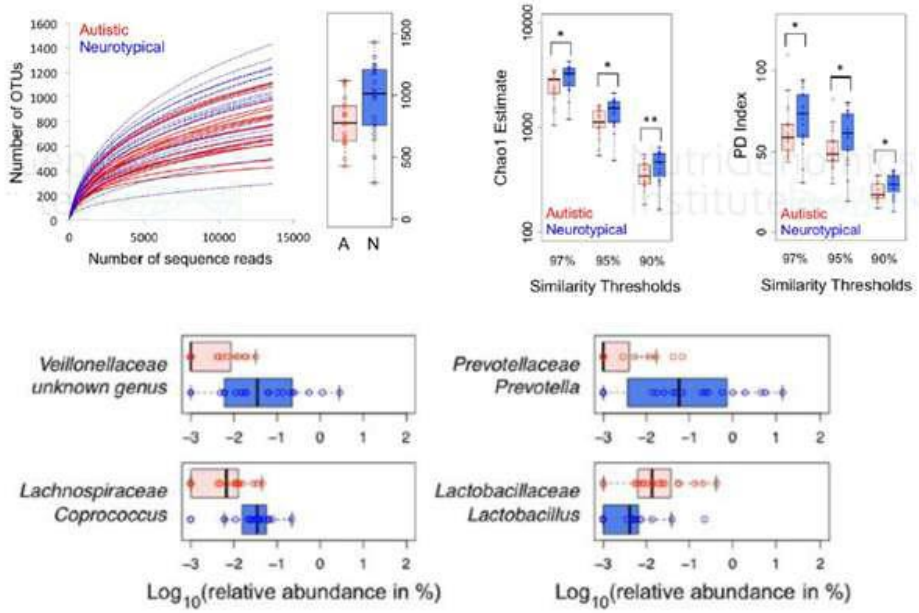
MICROBIOTA AND NEURODELOPMENTAL DISORDERS

AUTISM SPECTRUM DISORDER

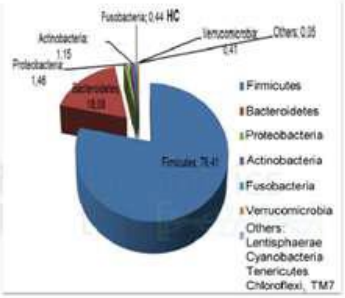
1. Neurobiological disorder whose main manifestations are a great inability to interact and communicate as well as restrictive and repetitive behaviour patterns.
2. Unknown etiology: genetics, gene-environment interaction.
3. Gastrointestinal disorders are a common symptom in this type of disorder.

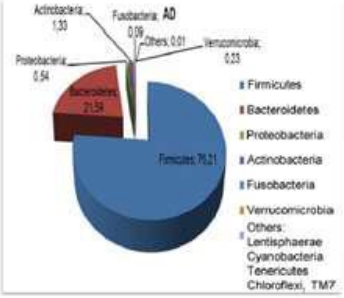
Reduced incidence of Prevotella and other fermenters in intestinal microflora of autistic children.

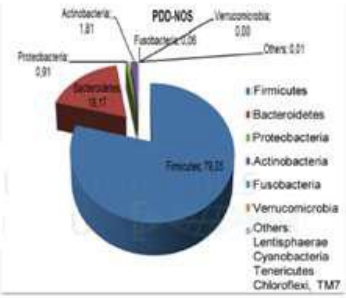


Kang et al. PLoSOne 2013, 8(7):e68322

Faecal Microbiota and Metabolome in children with Autism Disorder (AD) and Fecal y Metaboloma de niños con Autismo (AD) and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS)





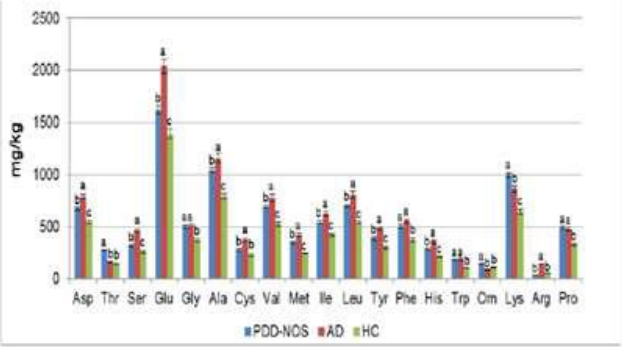


AD ↑ Clostridiaceae

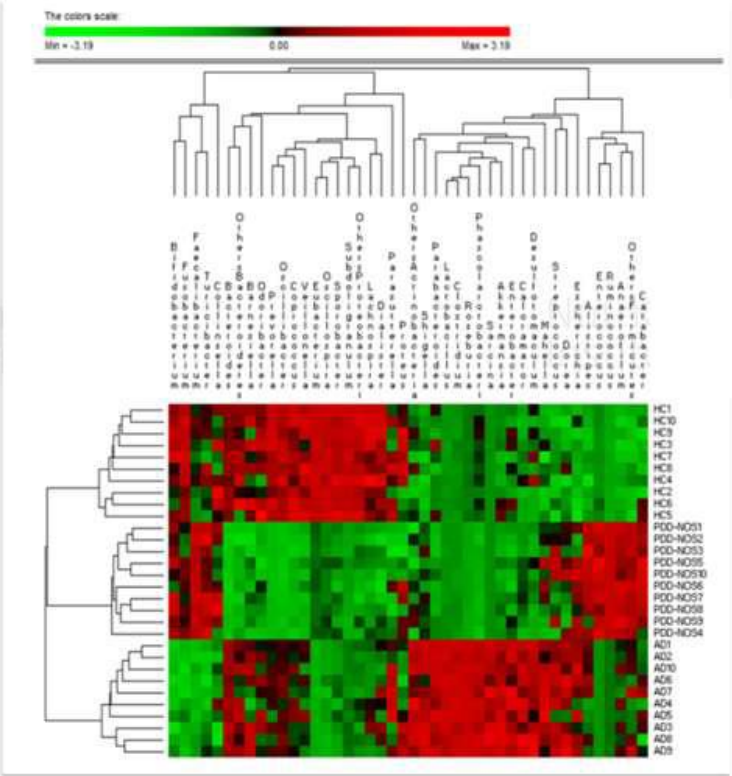
(fenols, p-cresol, indol derivatives)

Changes in Lachnospiraceae and lactic acid-fermenting bacteria

↑ Free Amino Acids



Angelis et al. 2013, Peer J, DOI 10.7717/peerj.1140



Angelis et al. 2013, Peer J, DOI 10.7717/peerj.1140

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MICROBIOTA AND MENTAL DISORDERS

SCHIZOPHRENIA

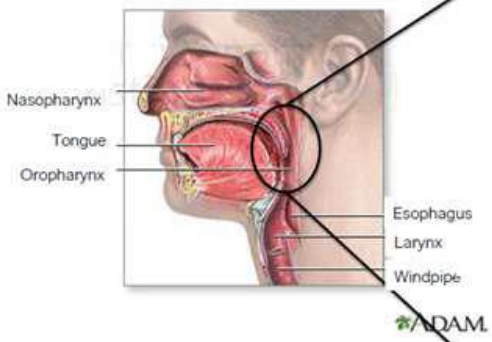
- Distortion of reality perception
- Etiology: genetics, social factors (stress), drugs, prenatal environment disruption.

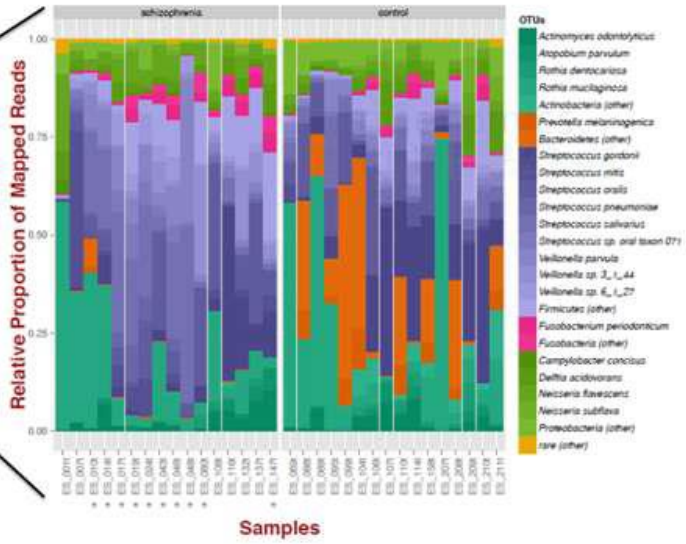
DEPRESSION

- Altered mood
- Associated to anxiety disorders.
- Influence of genetic, biological and psychosocial factors.

MICROBIOTA AND SCHIZOPHRENIA

Composition, taxonomy and functional diversity of the oropharyngeal microbiome in individuals with schizophrenia and controls



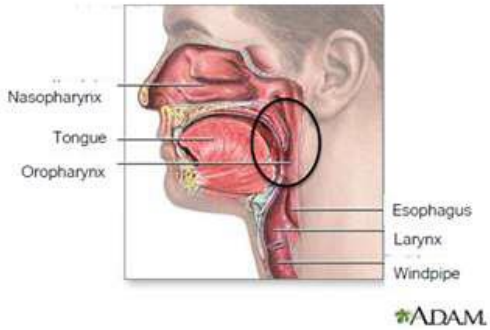


- Increase in Firmicutes
- Reduction in Bacteroidetes

Green: Actinobacteria, Orange: Bacteroidetes, Blue: Firmicutes, light green: Proteobacteria

Castro-Nallar et al. 2015, Peer J, DOI 10.7717/peerj.1140

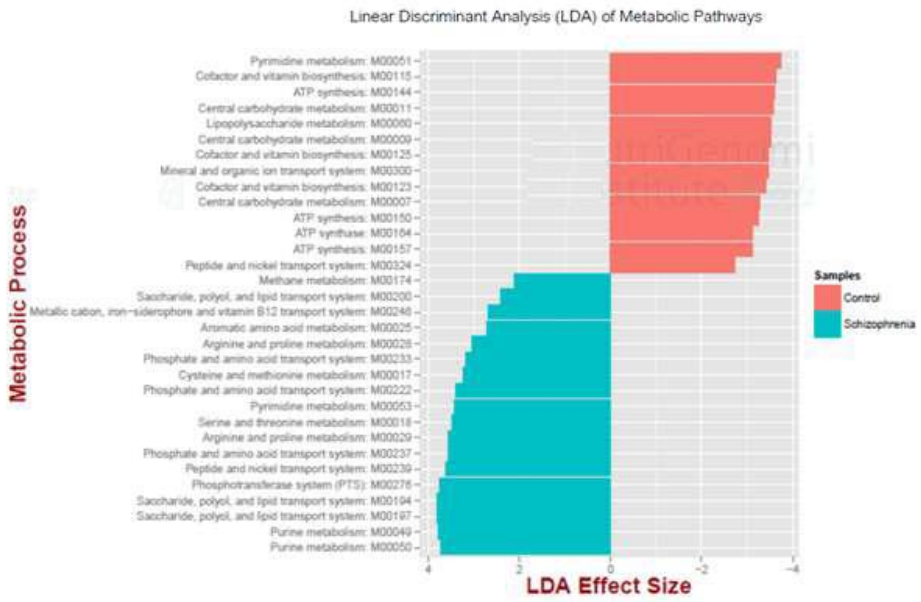
Oropharynx microbiome in schizophrenic patients: Increase in lactic acid producing species such as *Lactobacillus* y *Bifidobacterium*



Effect size (log2 fold change)	Effect size standard error	*p* value (BH adjusted)	Phylum	Genus	Species
8.37	1.17	2.55E−10	Firmicutes	*Lactobacillus*	*Lactobacillus gasseri*
6.81	0.99	9.61E−10	Firmicutes	*Catenibacterium*	*Catenibacterium mitsuokai*
4.82	0.99	3.94E−05	Firmicutes	*Eubacterium*	*Eubacterium hallii*
5.71	1.29	3.13E−04	Ascomycota	*Candida*	*Candida dubliniensis*
2.98	0.80	4.17E−03	Firmicutes	*Lactobacillus*	*Lactobacillus salivarius*
3.79	1.06	6.30E−03	Actinobacteria	*Bifidobacterium*	*Bifidobacterium pseudocatenulatum*

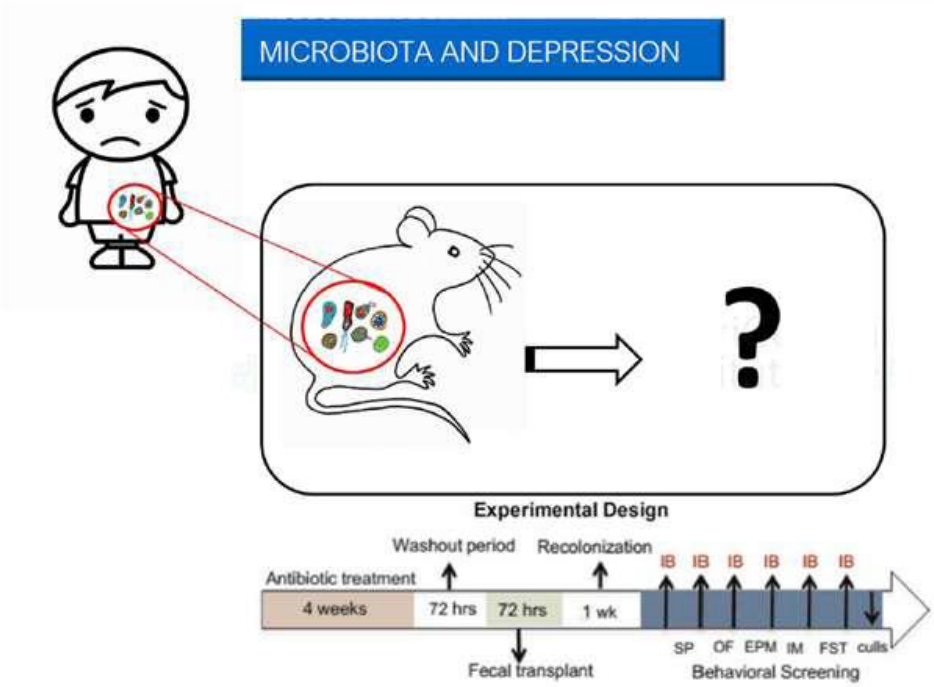
Castro-Nallar et al. 2015, Peer J, DOI 10.7717/peerj.1140

- Increase in Metabolic Pathways involved in the Transport of Metabolites and Amino Acid Metabolism
- Reduction in Lipid and Carbohydrate Pathways



Castro-Nallar et al. 2015, Peer J, DOI 10.7717/peerj.1140

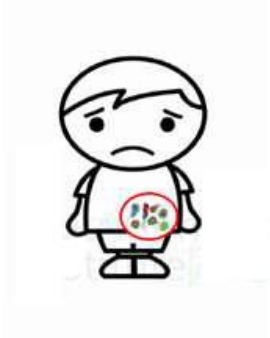
MICROBIOTA AND DEPRESSION

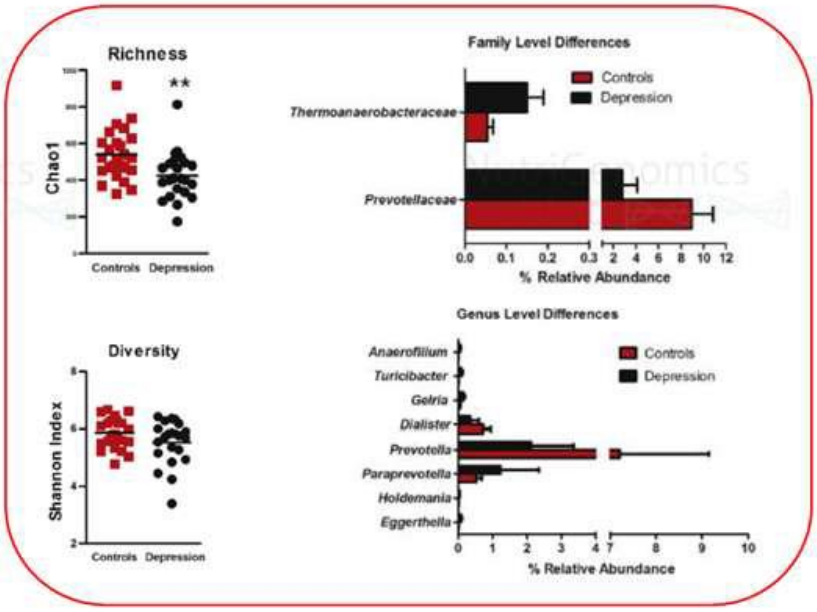


Transferring the blues: Depression-associated gut microbiota induces neurobehavioural changes in the rat

Kelly et al. Journal of Psychiatric Research, 2016, Vol 82: 109-118

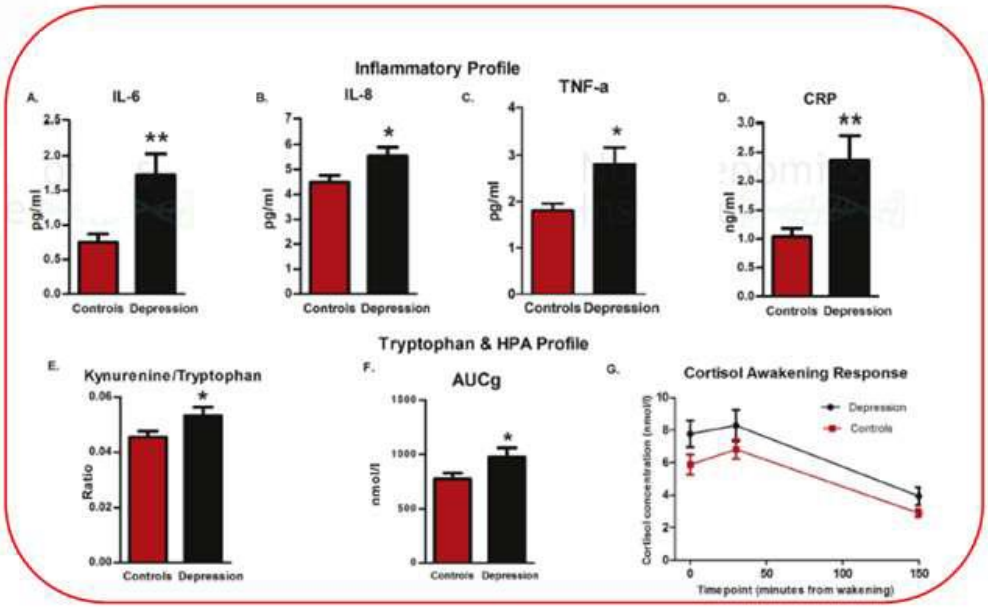
Lower abundance and diversity of microorganisms in the fecal microbiota of patients with depression





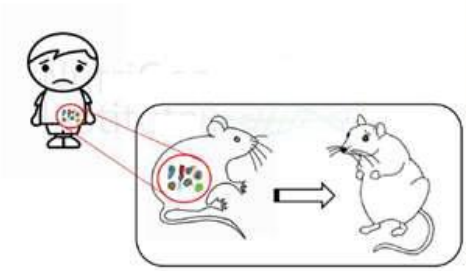
Kelly et al. Journal of Psychiatric Research, 2016, Vol 82: 109-118

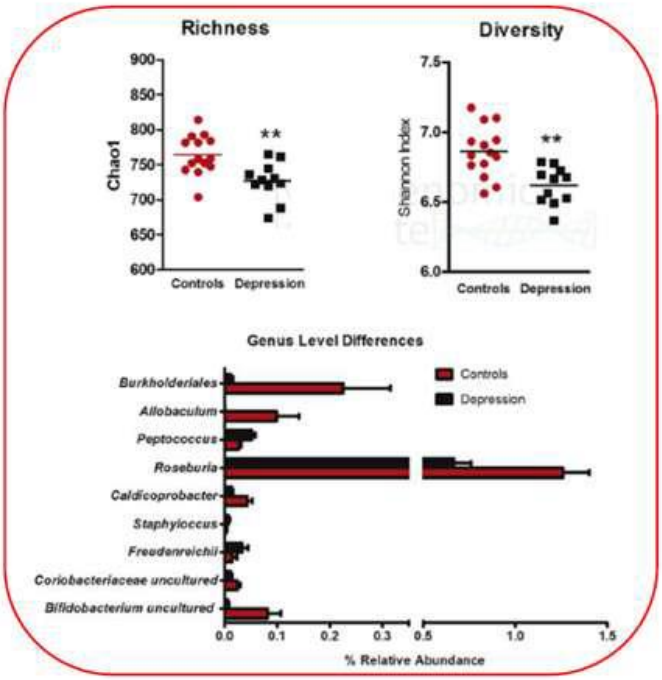
Inflammatory and stress response phenotype alteration in individuals with depressive disorder



Kelly et al. Journal of Psychiatric Research, 2016, Vol 82: 109-118

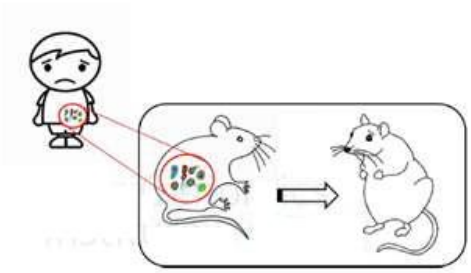
Recolonized mice show an altered microbiota composition after fecal transplant

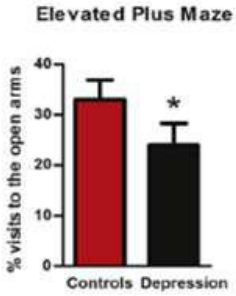


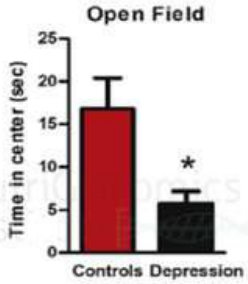


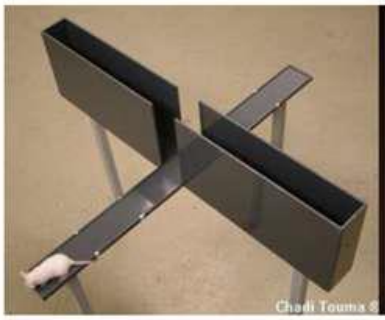
Kelly et al. Journal of Psychiatric Research, 2016, Vol 82: 109-118

Depression phenotype acquisition after fecal transplant









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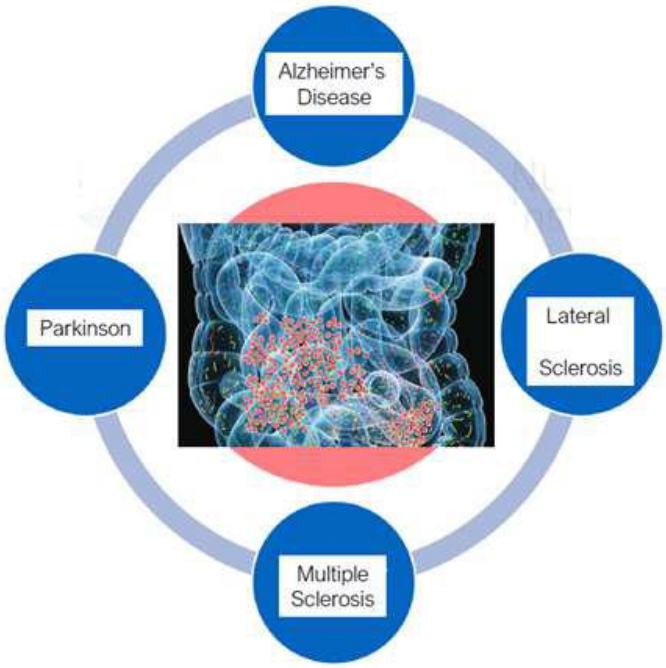
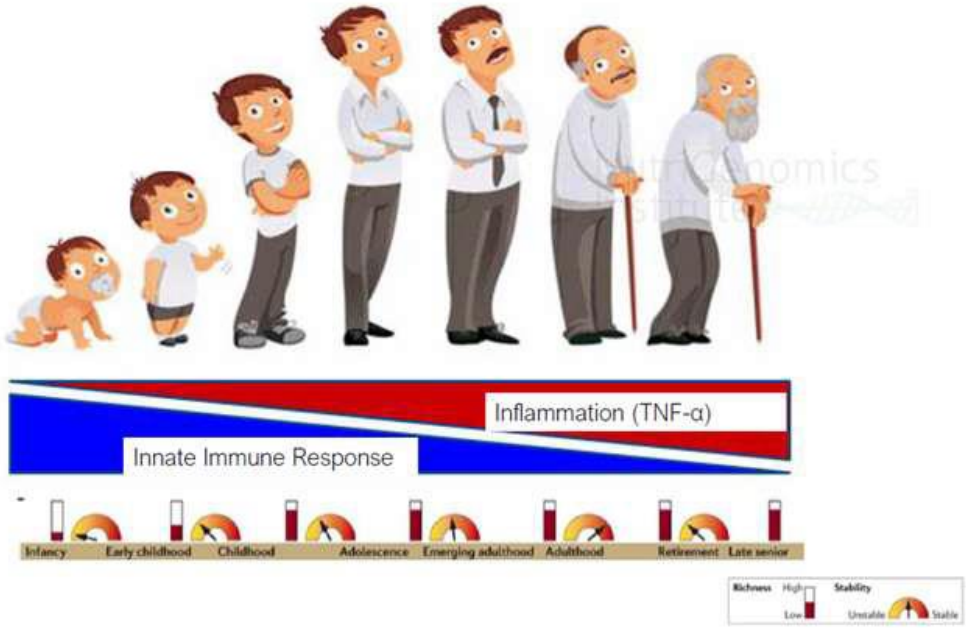
MICROBIOTA AND NEURODEGENERATIVE DISEASES

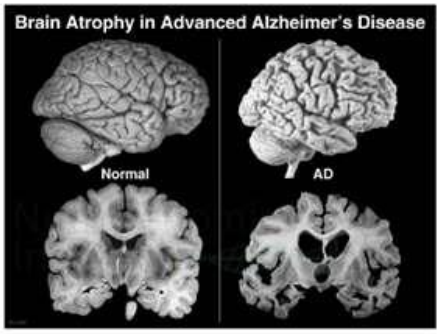


Degenerative Disorders

"Chronic Inflammation and Instability of the Microbiota"



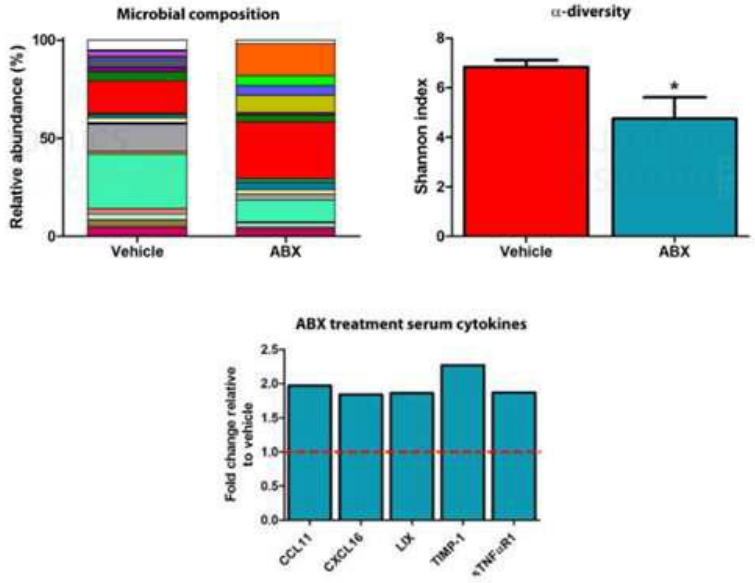
MICROBIOTA AND ALZHEIMER'S DISEASE



- Neurodegenerative disorder characterized by cognitive impairment and behavior disorders (short-term memory loss)
- Anatomically, neurofibrillary structures appear by the aggregation of beta amyloid peptide or Tau (senile plaques)
- Unkonw etiology, although it is believed to be a prion process.
  - Cholinergic hypothesis
  - Beta amyloid and Tau hypothesis
  - Metabolic disorder hypothesis: hyperglycemia and insulin resistance
  - There are inherited forms: mutations (APP, Presenilin 1, 2)

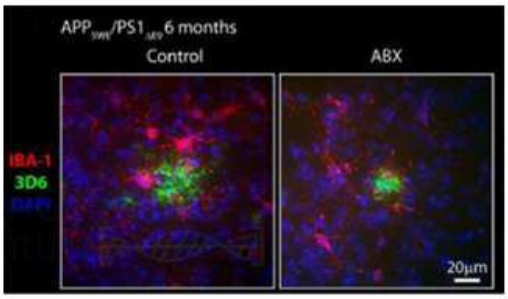
Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease

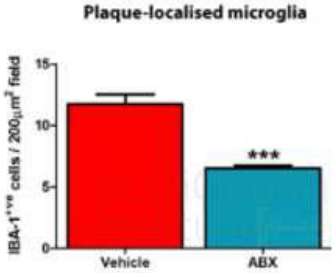
$APP_{SWE}/PS1_{\Delta E9}$ mice

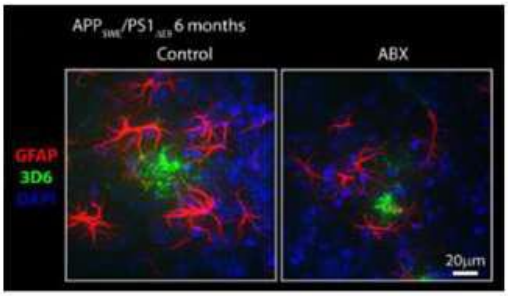


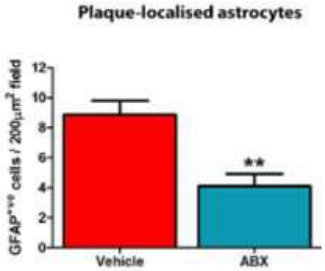
Minter et al. Scientific Reports, 2016. Jul 21;6:30028 doi: 10.1038/srep30028

Microbiota perturbation is related to a smaller infiltration of microglia and astrocytes in the amyloid plaque









Minter et al. Scientific Reports, 2016. Jul 21;6:30028 doi: 10.1038/srep30028

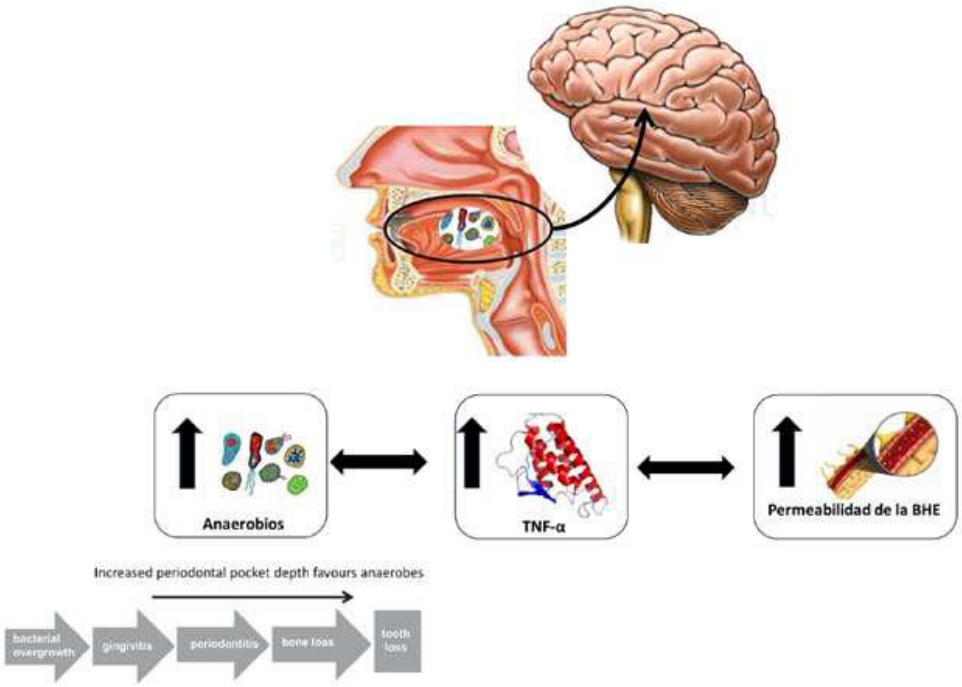
Serum IgG Antibody Levels to Periodontal Microbiota Are Associated with Incident Alzheimer Disease

- High anti-A. *naeslundii* titer (>640 ng/ml) was associated with increased risk of Alzheimer's Disease (HR=2,0, 95%:1,1-3,8)
- High anti-E. *nodatum* IgG (>1755 ng/ml) was associated with lower risk of Alzheimer's Disease (HR=0,5, 95%CI:0,2-0,9)

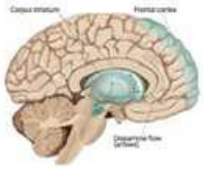
Noble et al. PLoS One, 2014. Dec 18;9(12):e114959. doi: 10.1371/journal.pone.0114959

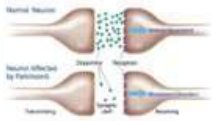
Link between Oral Microbiome, Aging and Alzheimer's

Shoemark and Allen. Journal of Alzheimer's Disease, 2015. 43:725-738



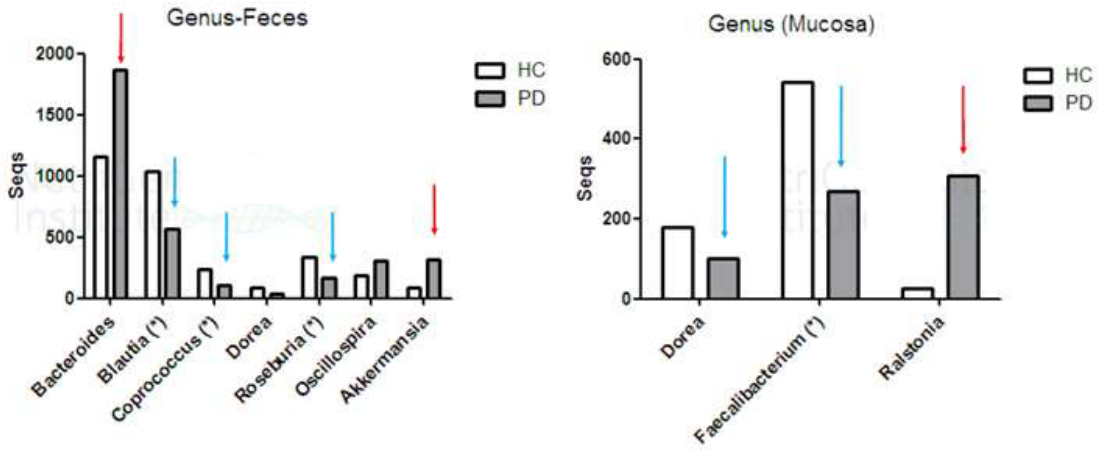
MICROBIOTA AND PARKINSON'S DISEASE





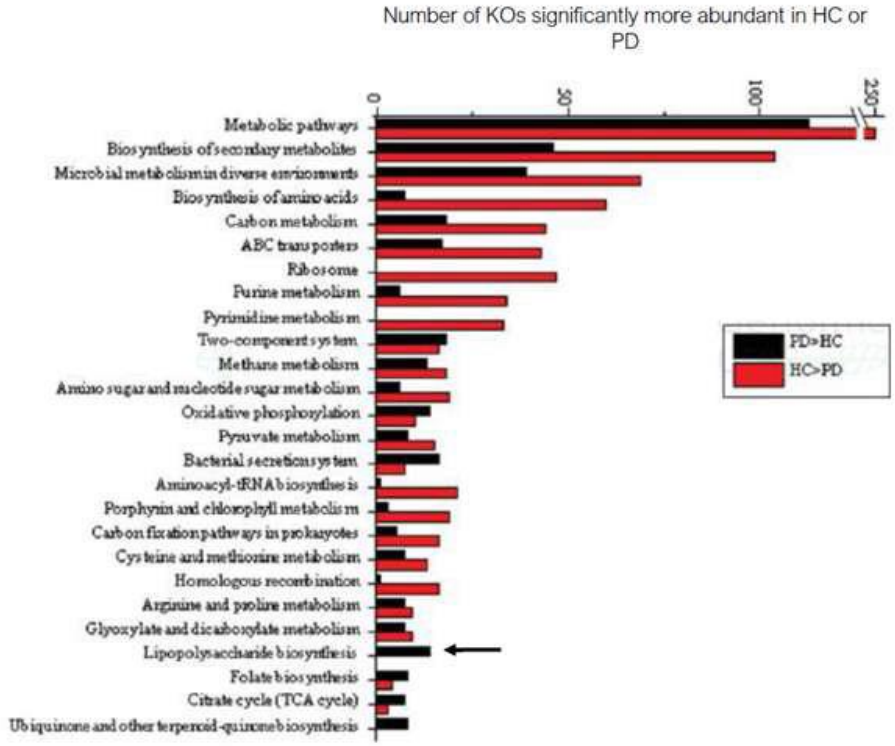
- Neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra (SN).
- Characteristic appearance of α-synuclein aggregates in the so-called Lewy bodies.
- Affected individuals show cognitive, emotional and autonomous disorders. The most common symptoms are resting tremor, muscular hypertonia, loss of postural reflexes and segmental cephalic tremor, among others.
- Unknown etiology, possibly multifactorial.

Colonic bacterial composition in Parkinson's Disease



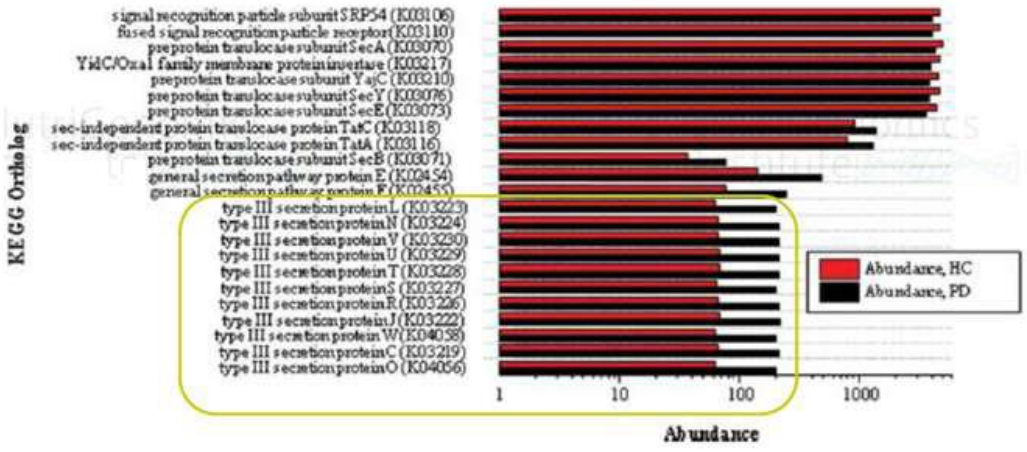
Reduction in butyrate producing bacteria present in the feces and increase of pro-inflammatory bacteria in the colonic mucosa.

Keshavarzian et al. Movement Disorder, 2015. 30(10: 1351-1360



Keshavarzian et al. Movement Disorder, 2015. 30(10: 1351-1360

Reduction in genes involved in the metabolism and increase in genes related to polysaccharide synthesis and bacterial secretion

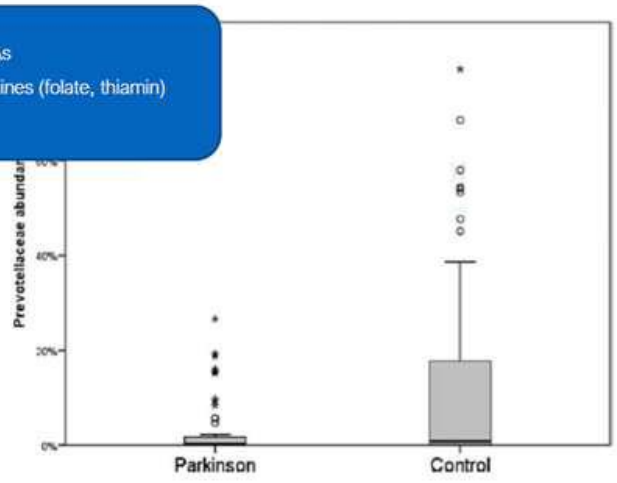


Keshavarzian et al. Movement Disorder, 2015. 30(10: 1351-1360

Relationship of gut microbiota and the clinic phenotype in Parkinson's Disease

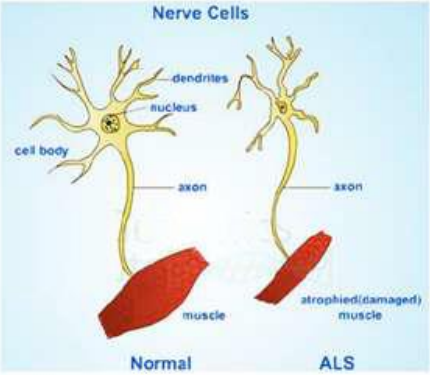
Family	Control vs. PD
Prevotellaceae	1.490 [1.005–1.976], 36.179, <0.001
Lactobacillaceae	−5.095 [−6.190 - −4.000], 83.151, <0.001
Verrucomicrobiaceae	−1.126 [−1.784 - −0.468], 11.254, 0.001
Bradyrhizobiaceae	−2.368 [−3.069 - −1.666], 43.748, <0.001
Clostridiales Incertae Sedis IV	1.441 [0.613–2.269], 11.628, 0.001
Ruminococcaceae	−52.526 [−317.204–212.151], 0.151, 0.697

- SCFAs
- Vitamines (folate; thiamin)
- H_2S



Scherpojan et al. Movement Disorder, 2015. 30(3): 350-358

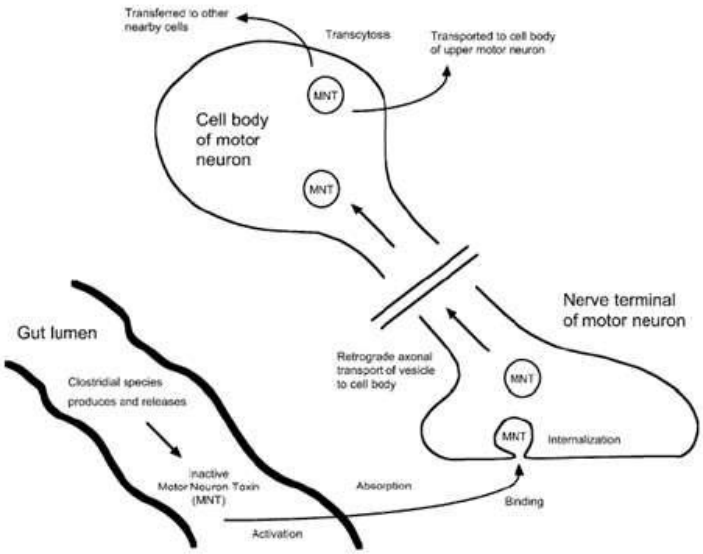
MICROBIOTA AND AMYOTROPHIC Lateral Sclerosis (ALS)



- Neurodegenerative disorder characterized by the progressive loss of motor neurons in the cortex, brainstem and spinal cord.
- Affected individuals suffer from a progressive atrophy and weakness of skeletal, spinal and bulbar muscles, which eventually leads to death.
- There are variants: Existen variantes: juvenile and infantile spinal muscular atrophy, primary Lateral Sclerosis, spinal and bulbar muscular atrophy.
- Unknown etiology, possibly MULTIFACTORIAL
  - Familiar (5-10%): SOD, TARDBP, C9orf72
  - Sporadic (90-95%)

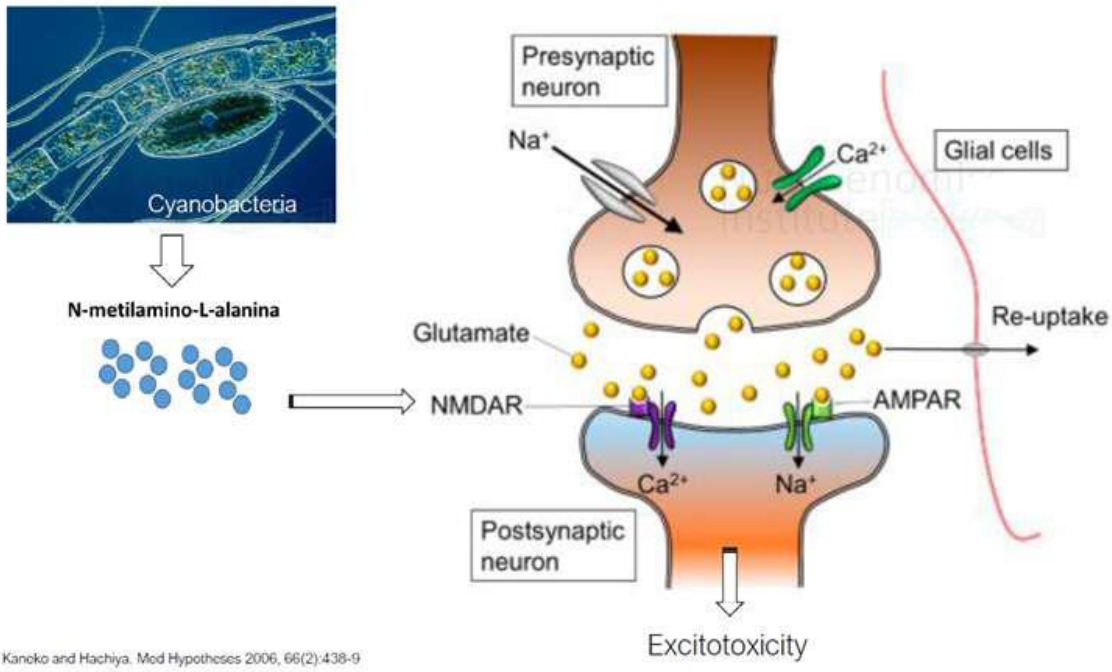
Hypothesis: A motor neuron toxin produced by a clostridial species residing in gut causes ALS

W.T. Longstreth Jr.[a,b,c,*], J.S. Meschke[d], S.K. Davidson[e], L.M. Smoot[e], J.C. Smoot[e], T.D. Koepsell[b,c,f]



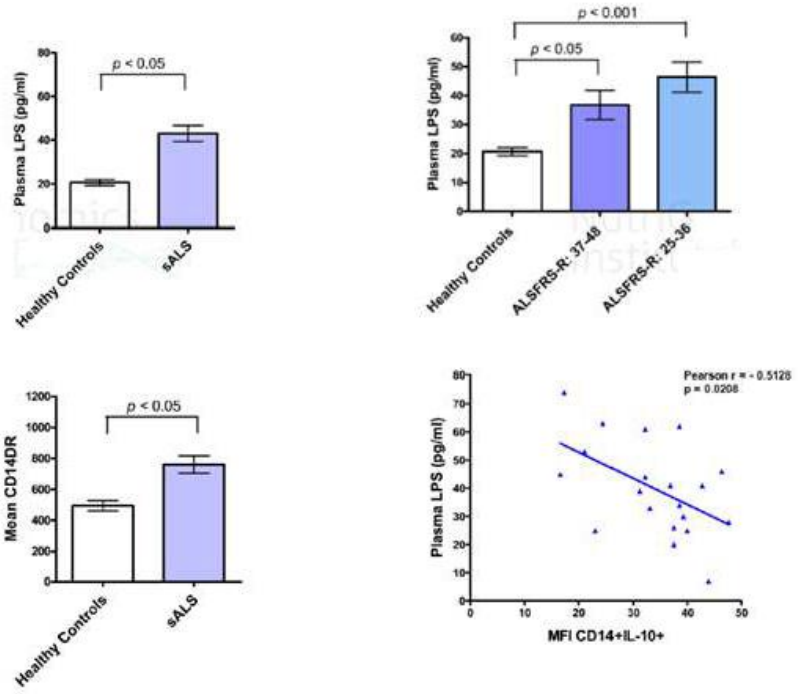
Longstreth et al. Medical Hypotheses (2005) 64, 1153-1156

Hypothesis: Gut as source of motor neuron toxin in the development of ALS



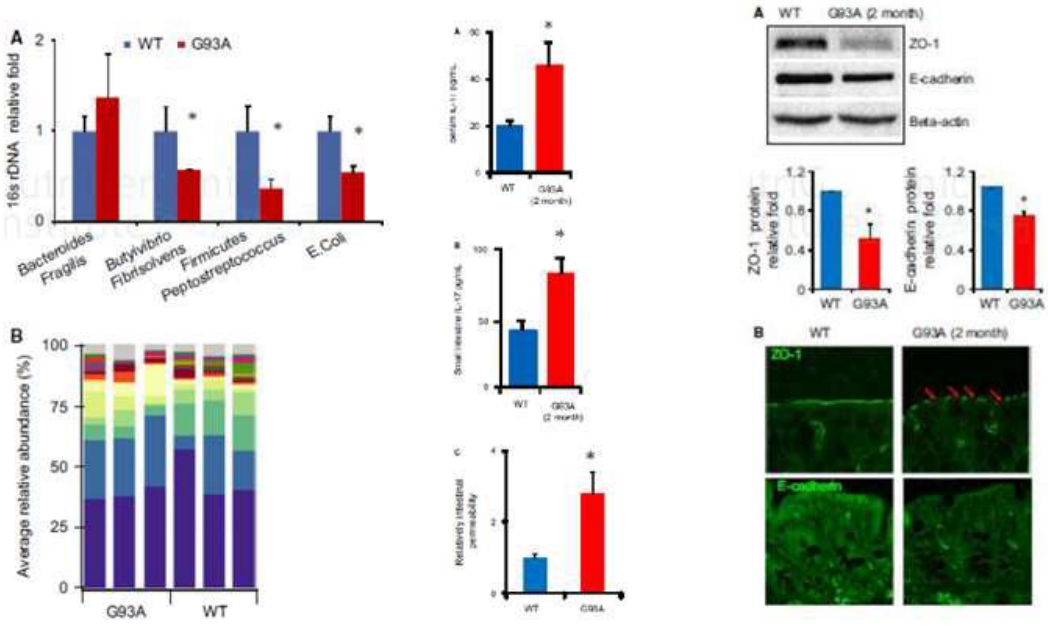
Kanoko and Hachiya. Med Hypotheses 2006, 66(2):438-9

Circulating endotoxemia and immune system activation in sporadic ALS



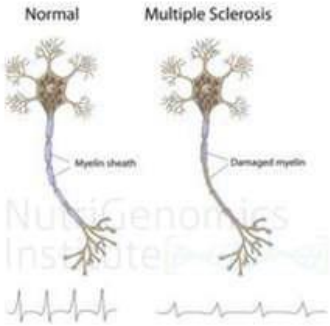
Zhang et al. Journal Neuroimmunology , 2009. 3; 206 (1-2): 121-124

Leaky gut and microbiome alteration in a Amyotrophic Lateral Sclerosis model (SOD^{G93A})



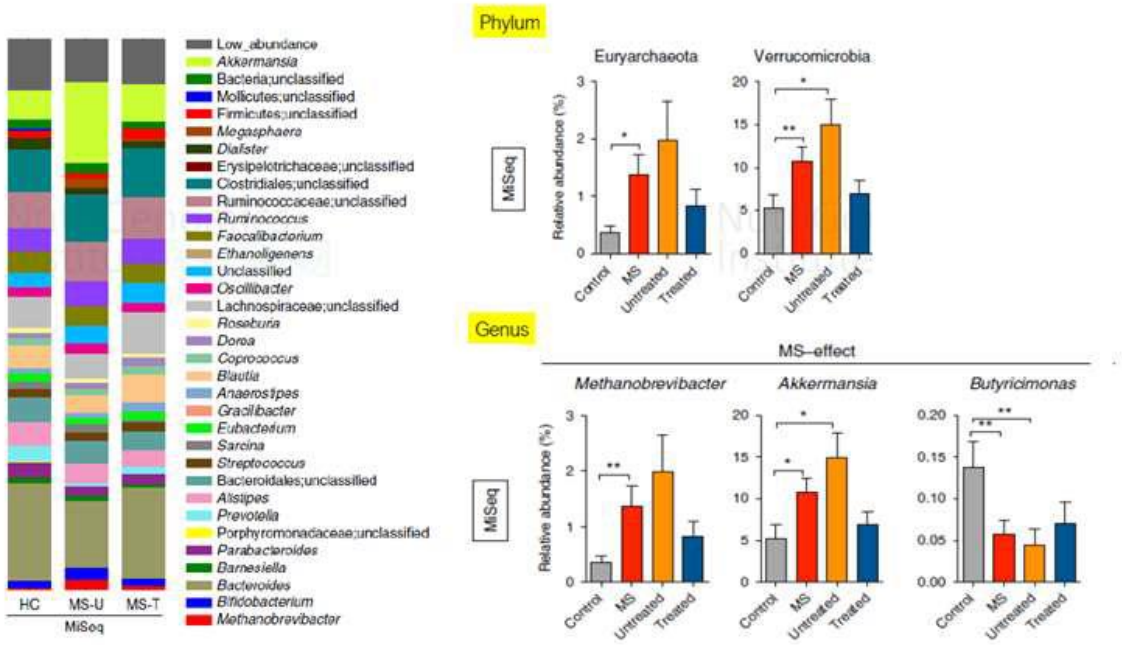
Wu et al. Physiol Rep , 2015

MICROBIOTA AND MULTIPLE SCLEROSIS



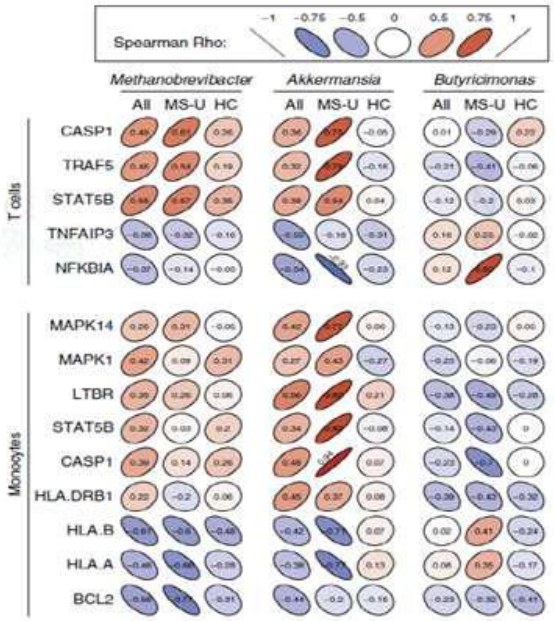
- Chronic Central Nervous System Disease of an autoimmune nature, which affects the brain's myeline and the spinal cord.
- Coordination and balance problems, muscular weakness, vision disturbances, difficulty in thinking and memorizing, itching sensation, numbness…
- Unknown etiology
  - Genetic factors: 200 genes identified
  - Environmental factors: smoking, lack of vitamin D

Human gut microbiota alterations in Multiple Sclerosis



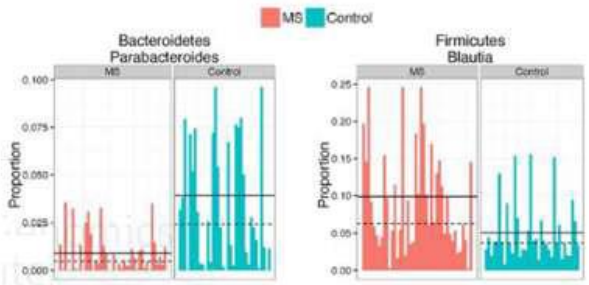
Jangi et al. Nature Communication, 2016. Jun 18; 7:12015 doi: 10.1038/ncomms12015

Correlation of differential fecal microbiota in patients with Multiple Sclerosis and its inflammatory phenotype



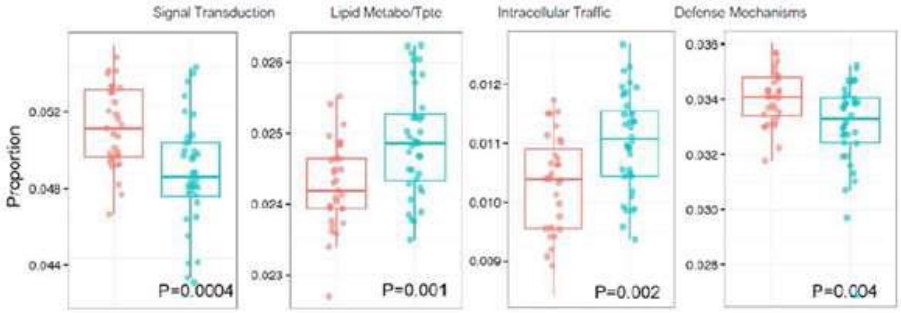
Jangi et al. Nature Communication, 2016. Jun 18; 7:12015 doi: 10.1038/ncomms12015

Human fecal microbiota differences in Multiple Sclerosis



Increase
- *Pseudomones*
- *Mycoplana*
- *Haemophilus*
- *Blautia*
- *Dorea*

Decrease
- *Parabacteroides*
- *Adlercreutzia*
- *Prevotella*



Chen et al. Nature Communication, 2016. Jun 18; 7:12015 doi: 10.1038/ncomms12015

MICROBIOTA AND NERVOUS SYSTEM DISEASES

1. Introduction
2. "Microbiota-gut-brain" axis: role of the microbiota in the development and physiology of the nervous system
   - "Microbiota-gut-brain" axis
   - Signalling pathways
   - Concept of leaky gut and role in neurological disorders
   - Study models: importance of axenic mice for the understanding of the molecular mechanisms associated
   - Temporal nervous system "windows of vulnerability" to the action of microbiota
   - Importance of maternal microbiota during pre-natal period and early post-natal life
3. Microbiota and Neurodevelopmental Disorders
   - Autism spectrum disorder
4. Microbiota and Mental Disorders
   - Schizophrenia
   - Depression
5. Microbiota and Neurodegenerative Disorders
   - Chronic inflammation associated to aging and instability of the microbiota
   - Alzheimer's Disease (AD)
   - Parkinson's Disease (PD)
   - Amyotrophic Lateral Sclerosis (ALS)
   - Multiple Sclerosis (MS)
6. **Gut microbiota modulation as a therapeutic strategy in Nervous System Diseases: use of prebiotics and/or probiotics**

GUT MICROBIOTA MODULATION AS A THERAPEUTIC STRATEGY IN NERVOUS SYSTEM DISEASES

Maternal diet-induced social and synaptic deficits can be reversed by means of microbial reconstruction

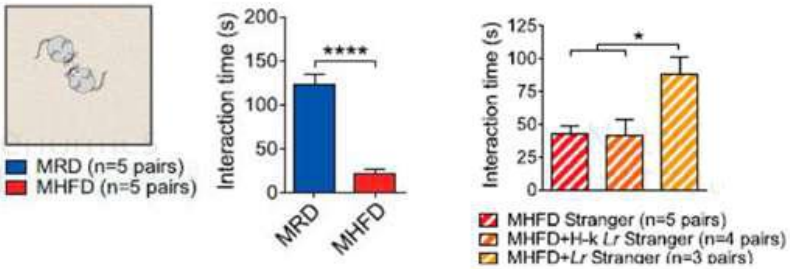


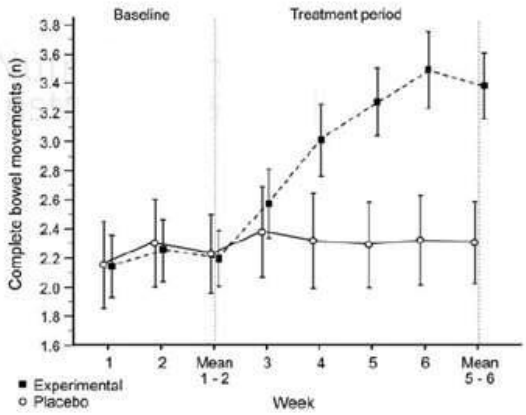
Table 1. Species Whose Abundance Is Reduced in the Gut Microbiota of MHFD Offspring

Species of Interest	MRD Representation	MHFD Representation
Lactobacillus reuteri	7.49 ± 3.0	0.879 ± 0.21
Parabacteroides distasonis	0.00709 ± 0.0055	0.00126 ± 0.0011
Helicobacter hepaticus	7.35 ± 2.4	2.58 ± 1.3
Bacteroides uniformis	5.49 ± 2.2	2.07 ± 0.78
Olsenella unclassified	0.230 ± 0.064	0.121 ± 0.031
Collinsella unclassified	0.0866 ± 0.031	0.0494 ± 0.016
Bifidobacterium pseudolongum	19.4 ± 3.3	11.3 ± 2.4
Lactobacillus johnsonii	24.5 ± 6.2	17.1 ± 5.2

Buffington et al. Cell 2016 Jun16: 165(7): 1762-75

Improvement of intestinal constipation in patients with Parkinson's Disease using a combination of a blend of probiotics and fiber

Complete bowel movements during the study



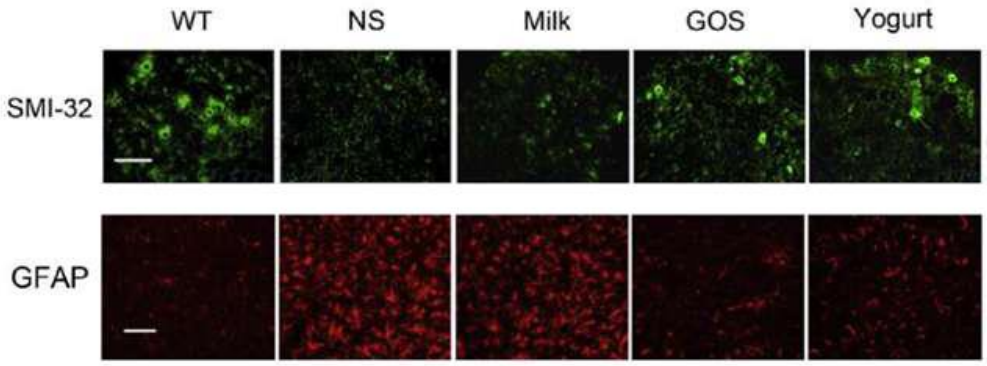
Composition of the interventions

	Fermented milk containing probiotics and prebiotic fiber (125 g)	Placebo (pasteurized fermented milk) (125 g)
Energy, kcal	75	77
Proteins, g	2.8	3.5
Carbohydrates, g	12.6	13.4
Fats, g	0.9	1.1
Fiber, g	7.8	0.26
Fructooligosaccharides, g	2.4	—
Calcium, mg	104	131
Phosphorus, mg	81	105
Probiotics,* CFU	250×10^9	—

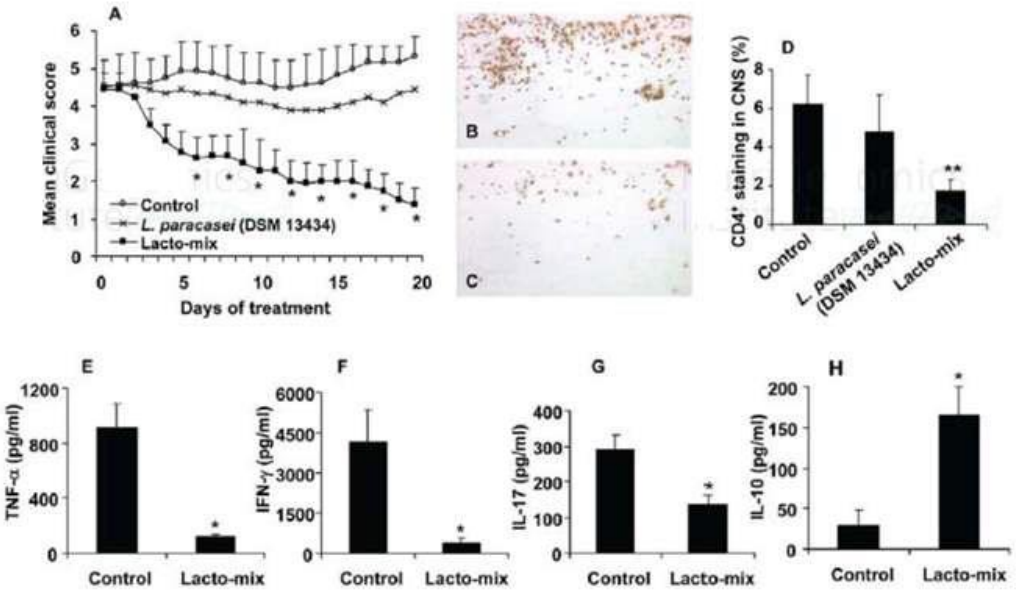
Abbreviation: CFU = colony-forming unit.
Interventions shelf life: 37 days (to be stored between 0°C and 4°C).
*Including the following strains: *Streptococcus salivarius* subsp *thermophilus*, *Enterococcus faecium*, *Lactobacillus rhamnosus GG*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus delbrueckii* subsp *bulgaricus*, and *Bifidobacterium breve* and *animalis* subsp *lactis*.

Barichella et al. Neurology, 2016. 87

Galactooligosaccharide improves survival and alleviates motor neuron death in SOD1G93A mouse model of amyotrophic lateral disease (ALS)



Mixture of Lactobacillus strains improves Autoimmune Encephalomyelitis



Lavasani S et al. PLoS One, 2010. Feb2; 5(2):e9009 doi: 10.1371/journal.pone.0009009

GENERAL CONCLUSIONS

1. The composition of gut microbiota can affect the development and physiology of the Nervous System through the "microbiota-gut-brain" axis.
2. The Nervous System "window of vulnerability" to the action of the microbiota takes place during all the lifespan.
3. Neurodevelopmental disorders and mental disorders can be related to alterations in the maternal gut microbiota and early factors affecting the colonization process.
4. Neurodegenerative disorders present a chronic inflammation that can be related to the alteration of the gut microbiota or the oral microbiota.
5. The reconstitution of the gut microbiota balance by means of probiotics appears as a powerful therapeutic strategy against neurological diseases.

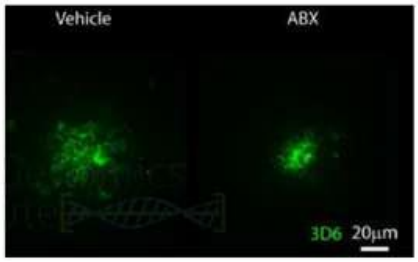
Supplementation with Probiotics as a therapeutic strategy in infantile Autism

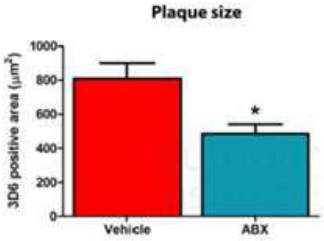
Author/year	Study group	Study design and level of evidence	Clinical outcomes	Results	Comments
Kaluzna-Czaplinska and Blaszczyk 2012[2]	*Patients*: children with autism (n=22). *Intervention*: oral supplementation of *Lactobacillus acidophilus* strain twice daily for 2 months. *Controls*: self, before the treatmer	Cohort study Level 3	Level of concentration and ability to carry out order	Improvement in ability to concentrate and carry out orders on probiotic therapy but no difference in behavioural responses to other people's emo[illegible]	Risk of selection and performance bias was high
Adams *et al* 2011	Patients on probiotics (n=19) vs no probiotics (n=38) in a subgroup of patients with ASD *Intervention*: none	Case–control study Level 4	1. Outcome- to assess the severity of gastrointestinal symptoms in ASD. 2. Autism symptoms assessed with the ATEC	ATEC scores were not provided for probiotic or the control arm	The type of probiotic organism, dose, duration of supplementation is not provided
Parracho *et al* 2010[3]	n=62 *Intervention*: *Lactobacillus plantarum* WCSF1 for 12 weeks	Double-blind, placebo-controlled, crossover design Level 2	Behaviour scores were assessed using a questionnaire	Scores for disruptive antisocial behaviour, anxiety problems and communication disturbances were higher in the placebo group	Low risk for selection and performance bias in view of blinding. Very high dropout rates
Tomova *et al* 2015[4]	n=10 *Controls*: 9 siblings of autism and 10 unrelated controls. *Supplements*: combination of *Lactobacillus*, *Bifidobacter*, and *Streptococci*, three times a day for 4 months	Cohort study Level 3	Severity evaluated using CARS	CARS and behaviour not studied after probiotic supplementation	Risk of selection bias high

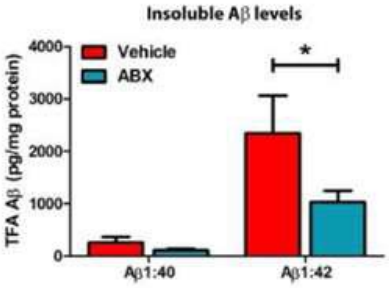
ASD, autism spectrum disorder; ATEC, Autism Treatment Evaluation Checklist; CARS, Childhood Autism Rating Scale.

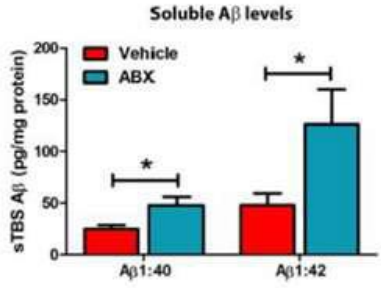
Srinivasjois et al 2015, Arch Dis Chield , 100(5):

Treated mice present a smaller plaque size, associated to higher levels of soluble beta amyloid

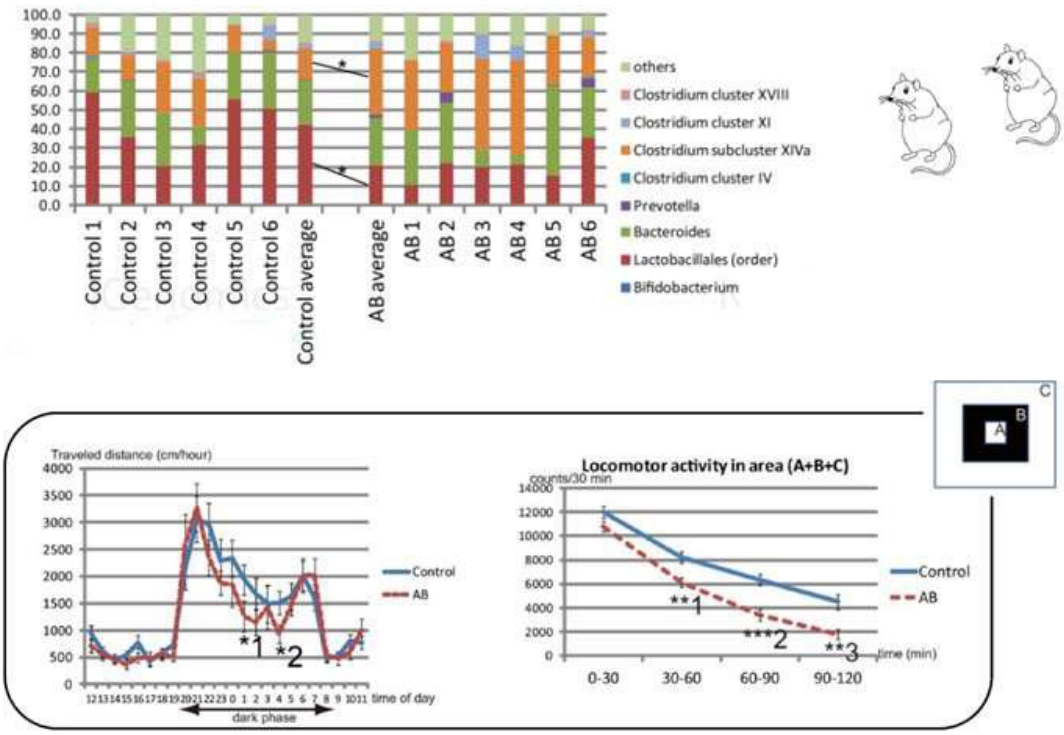








Minter et al. Scientific Reports, 2016. Jul 21;6:30028 doi: 10.1038/srep30028



Tochitani et al. PLoS One 2016: 11(1):e0138293

Groups of offspring

-Control:

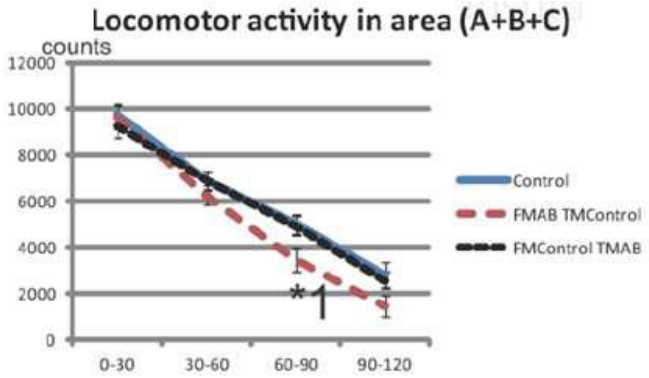
fostered by and born from Control dam

-FMAB TMControl:

fostered by AB-treated dam and born from Control dam

-FMControl TMAB:

fostered by Control dam and born from AB-treated dam



Tochitani et al. PLoS One 2016: 11(1):e0138293