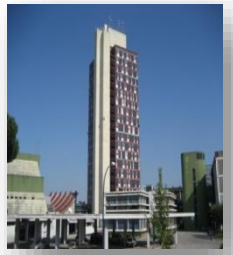

**GERARDO NARDONE**

# FRAGILITA' DEL CAVO ORALE
# EFFETTI DELL'INVECCHIAMENTO SUL MICROBIOTA

SOCIETÀ ITALIANA
DI GERONTOLOGIA
E GERIATRIA

Roma, 30 novembre - 3 dicembre 2022
UNIVERSITÀ CATTOLICA DEL SACRO CUORE

**Gastroenterology Unit**
**Department of Clinical Medicine and Surgery**
**University of Naples "Federico II"**



## Oral health

is an essential aspect of health, life satisfaction, quality of life, and self-perception

## Poor Oral health

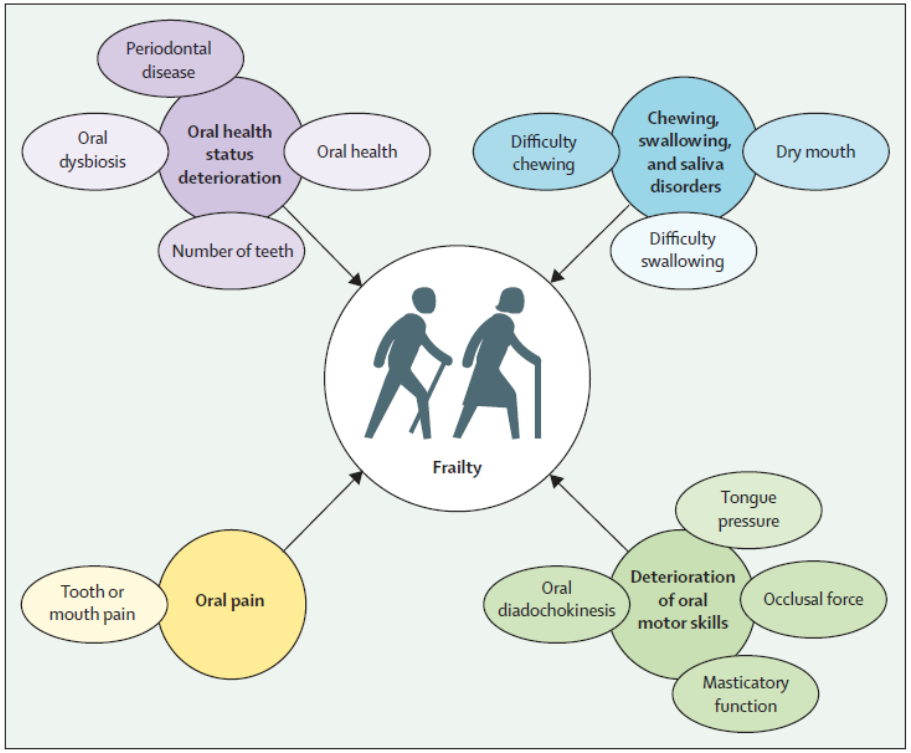
is common among older adults and influences oral function and daily activities

## Oral frailty

**is a decrease in oral function, food intake diversity, appetite, and nutrition**

The **Oral Frailty** phenotype
is a consequence of age-related gradual loss of oral function
eg.,

- **Loss of teeth**
- **Poor oral hygiene**
- **Inadequate dental prostheses**
- **Difficulty in chewing**
- **Changes in swallowing**




*V. Dibello, 2021*

International Journal of
*Environmental Research and Public Health*

MDPI

*Article*

# Associations between Oral Hypofunction Tests, Age, and Sex

**Oral hypofunction** is addressed by seven tests

- oral hygiene
- oral moisture
- occlusal force
- oral diadochokinesis
- tongue pressure
- masticatory function
- swallowing function

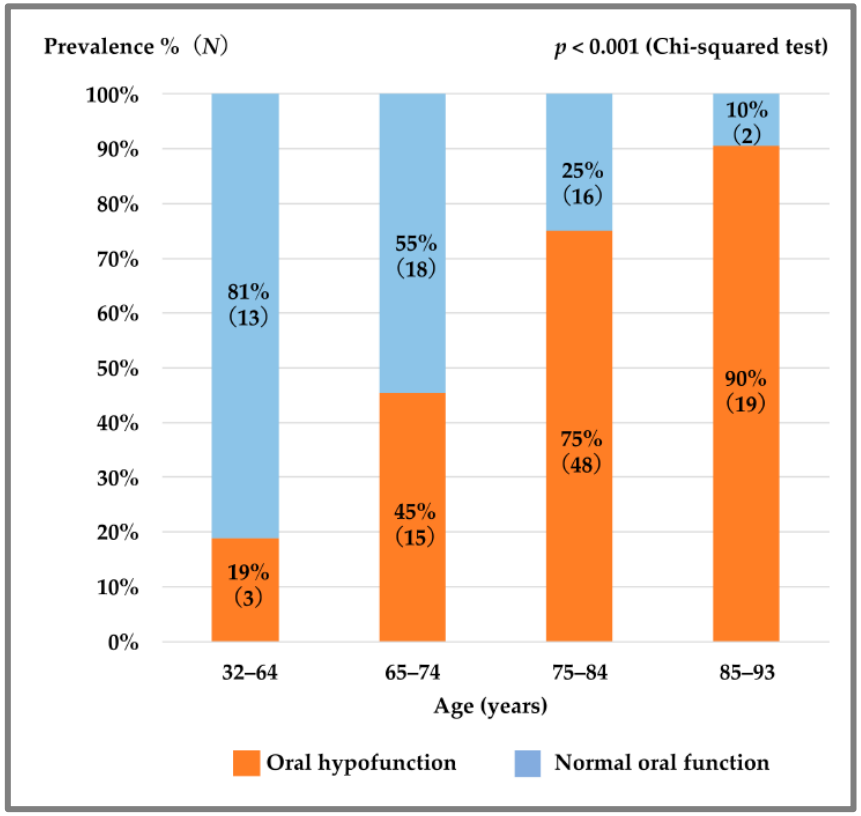
**Oral hypofunction**

Is diagnosed if

3/7 tests exceed

the reference values

**Oral hypofunction prevalence and age**




Oral hypofunction prevalence increased significantly with age zone

Yukiko Hatanaka, 2021

Oral Frailty Index-8 in the risk assessment of new-onset oral frailty and functional disability among community-dwelling older adults

Tomoki Tanaka [a], Hirohiko Hirano [b], Yuki Ohara [b], Misa Nishimoto [a], Katsuya Iijima [a,c,*]


2021

**Oral Frailty Index-8** (OFI-8), to help screen older adults at risk of oral frailty

## Oral Frailty Index-8

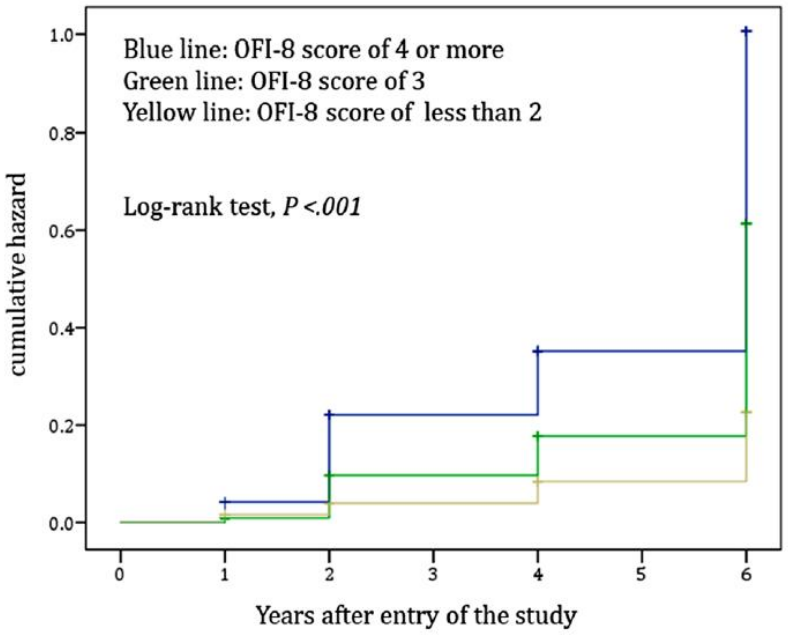
| | Yes | No |
|---|---|---|
| 1) Do you have any difficulties eating tough foods compared to 6 months ago? | +2 point | |
| 2) Have you choked on your tea or soup recently? | +2 point | |
| 3) Do you use dentures? [a] | +2 point | |
| 4) Do you often have a dry mouth? | +1 point | |
| 5) Do you go out less frequently than you did last year? | +1 point | |
| 6) Can you eat hard foods like squid jerky or pickled radish? | | +1 point |
| 7) How many times do you brush your teeth in a day? (3 or more times/day) | | +1 point |
| 8) Do you visit a dental clinic at least annually? | | +1 point |

2011 participants (51% women; mean age, 73.0 ± 5.5 years)

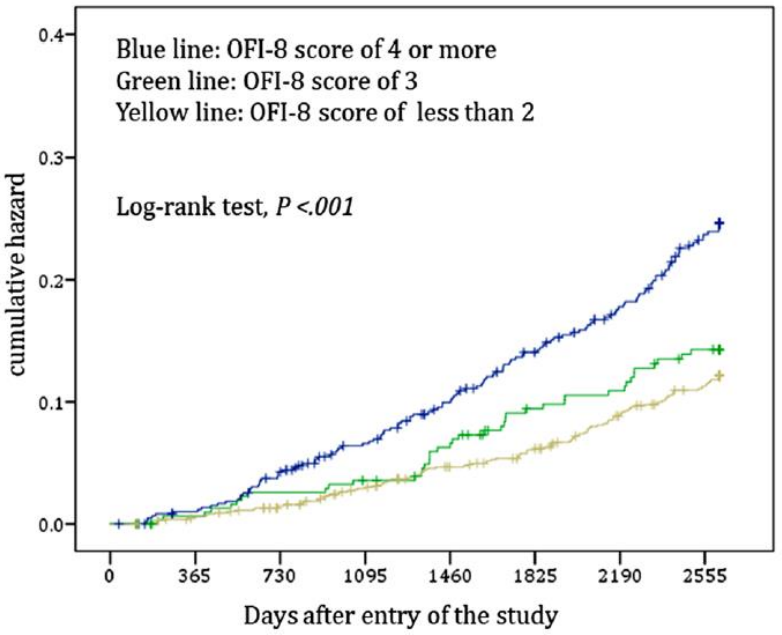
**1692 (84%)** without with oral frailty

**319 (16%)** with oral frailty

**New-onset of oral frailty**




**New needs for long term care**




**The OFI-8 score can effectively discriminate between participants**

**score of ≤ 4 points** are at a low risk for oral frailty

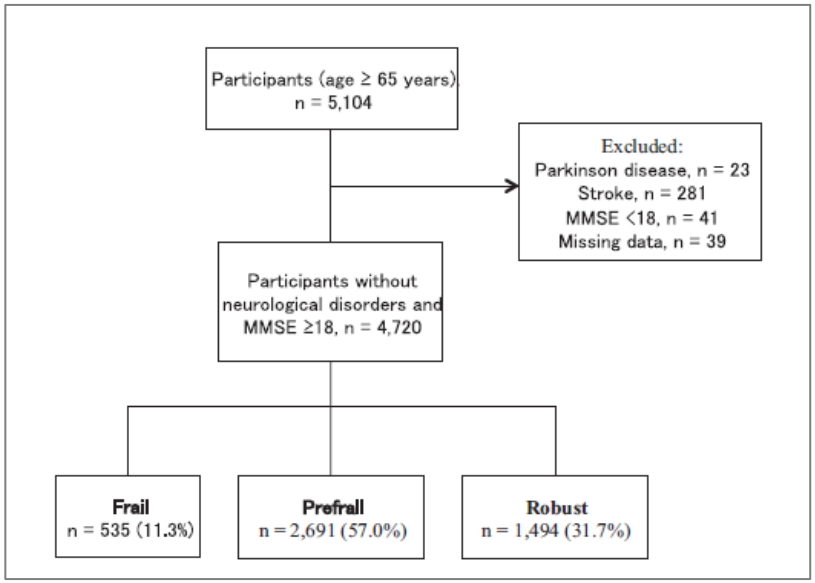
**score of ≥ 4 points** are at a high risk for new-onset oral frailty

need for long-term care

**Oral Frailty Index (OFI-8) may identify older adults at risk of oral frailty**


# Relationship Between Frailty and Oral Function in Community-Dwelling Elderly Adults

| | |
|---|---|
| **4,520** | **Elderly adults (≥65)** |
| 1,494 | Robust |
| 2,691 | Prefrail |
| **535** | **Frail** |



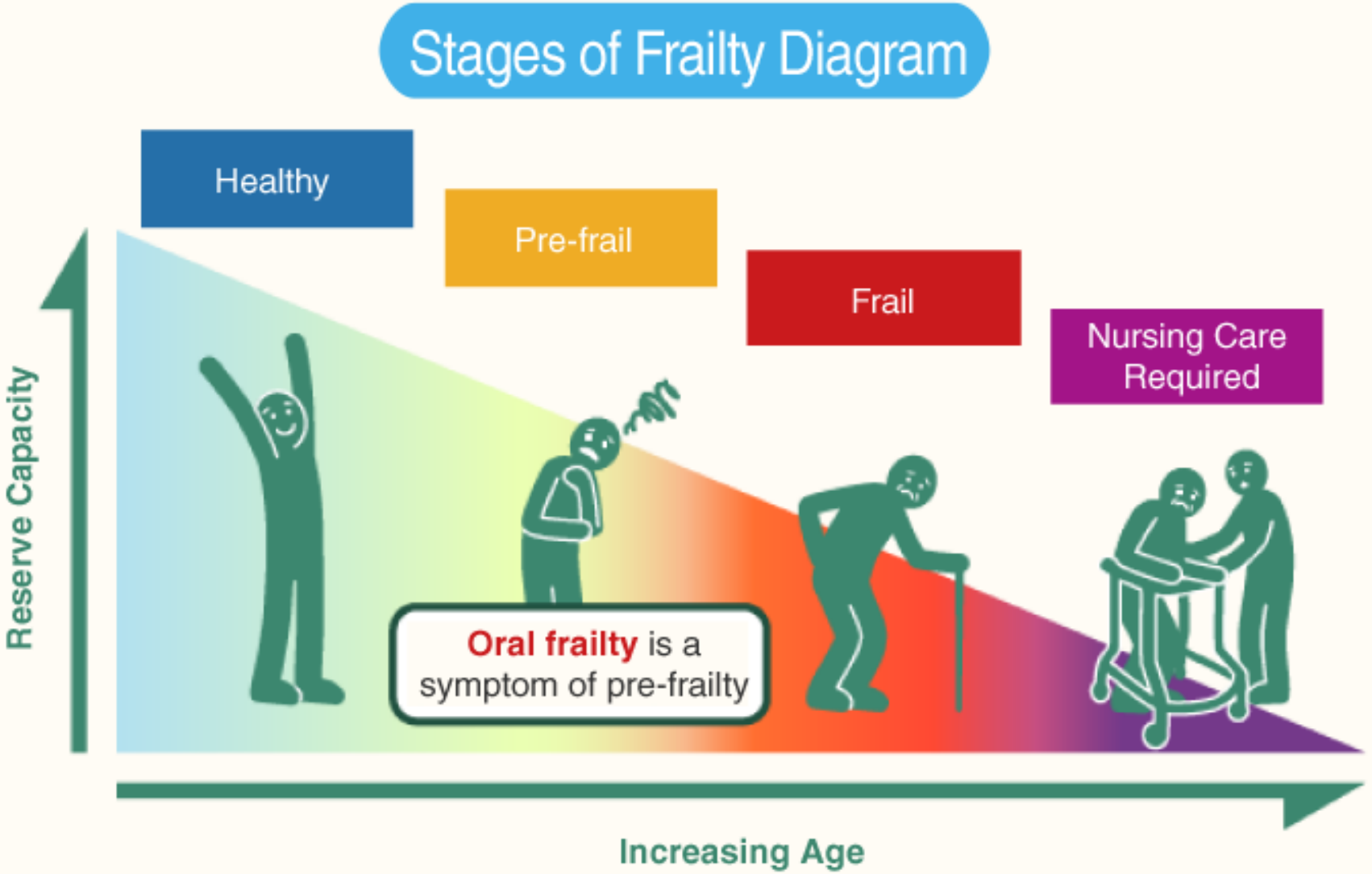

The Frail group had significantly

fewer present teeth (women aged ≥70),
lower occlusal force (women aged ≥70; men aged ≥80),
lower masseter muscle thickness,
lower oral diadochokinesis (ODK)

**Frail older** individuals had significantly poorer oral function than prefrail and robust individuals.

**The risk of frailty** was associated with lower occlusal force, masseter muscle thickness, and ODK rate.

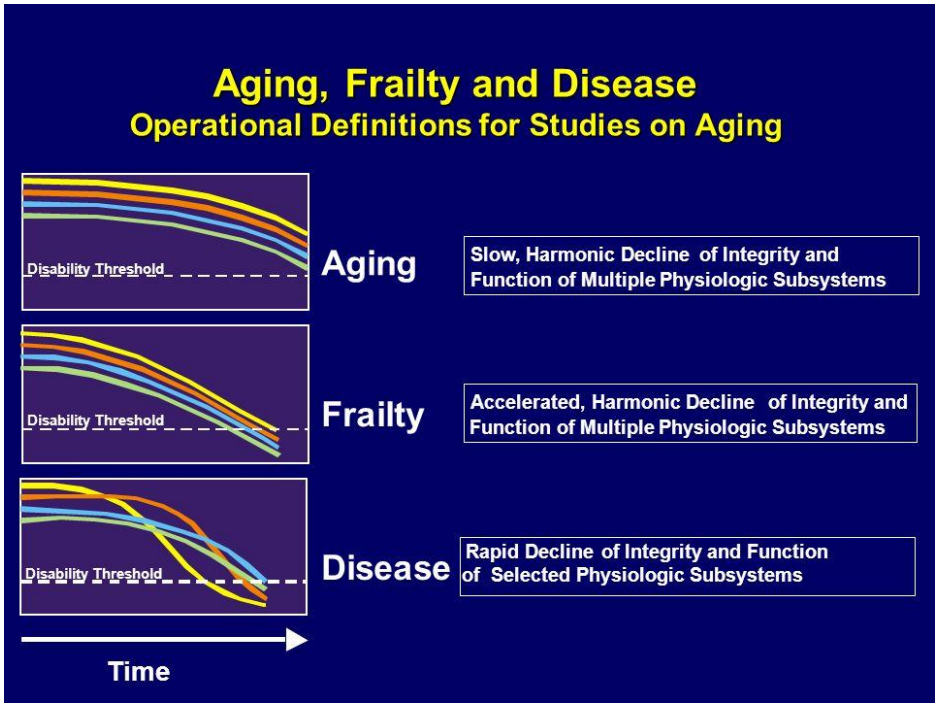
Yutaka Watanabe, 2016




Source: Prof. Katsuya Iijima, Institute of Gerontology, The University of Tokyo

**Oral frailty is defined by number of natural teeth, chewing ability, articulatory oral motor skill, tongue pressure, and subjective difficulties in eating and swallowing**

**Frailty is a state of accelerated decline in physical function and increased susceptibility to incident, hospitalization, and mortality**

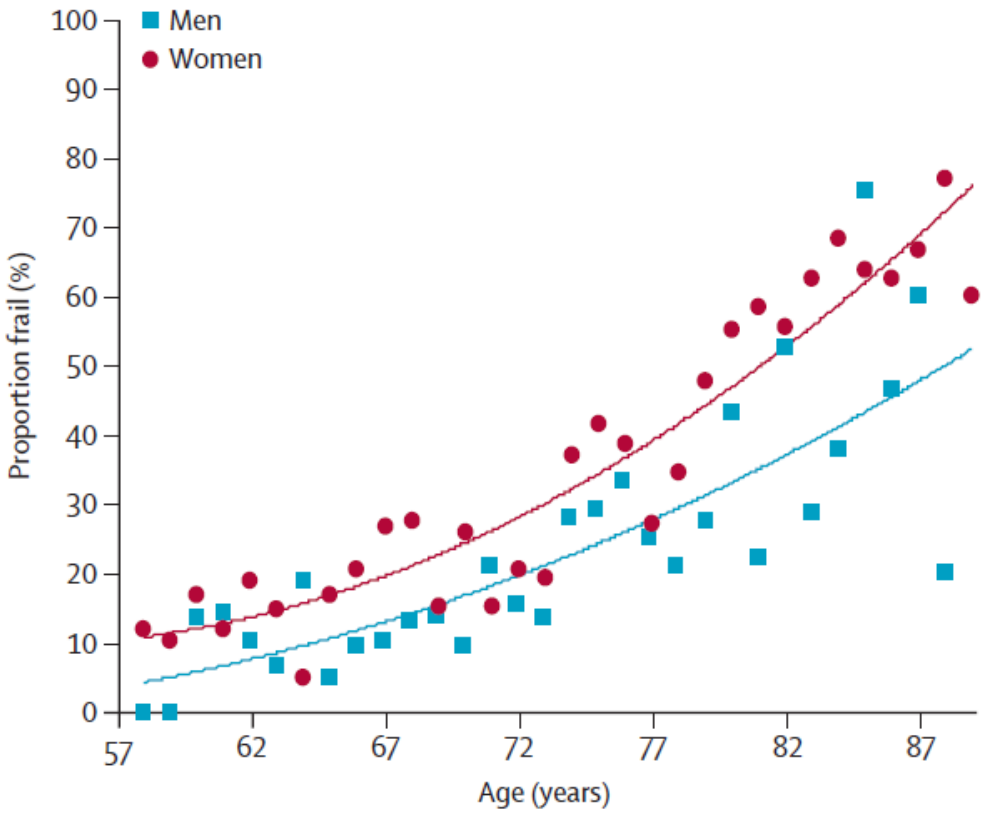



Groningen Frailty Indicators

- mobility
- physical fitness
- comorbidity
- weight loss
- vision
- hearing
- cognition
- psychosocial resources

Fried, *Geriatric , 2009*

# Ageing population and frailty



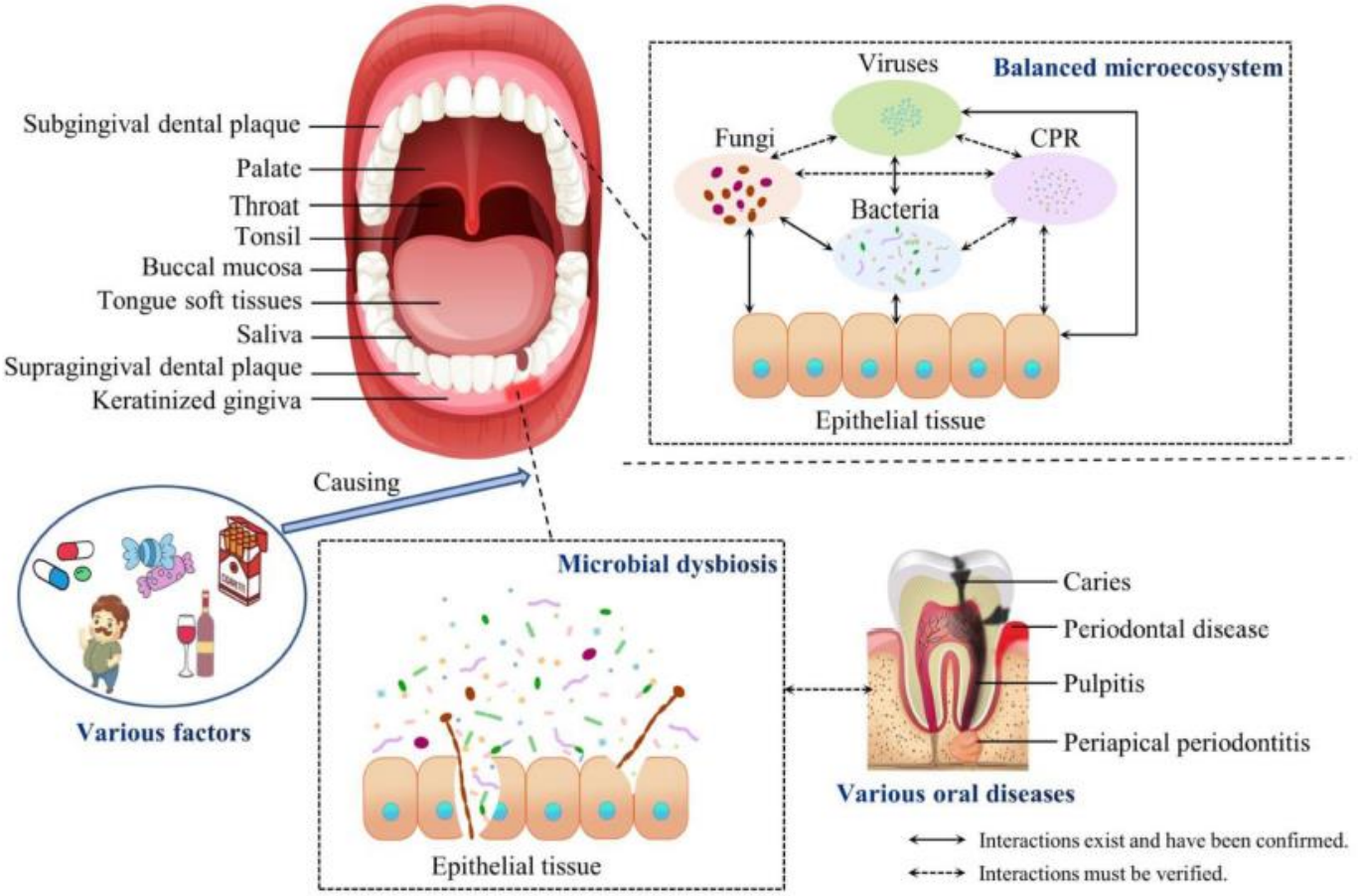

**Frailty occurs in adults at any age, but it is more prevalent in older women**

**The global impact of frailty is expected to increase due to population ageing**

**Frailty is an emerging global health burden, with major implications for clinical practice and public health**

Hoogendijk EO et al, The Lancet 2019

**The oral cavity is divided into 9 niches colonized by various microrganisms > 700 species**




**Oral microorganisms-host interactions maintain the oral microecosystem in a dynamic balance**

**but, if altered may contribute to oral and even systemic diseases**

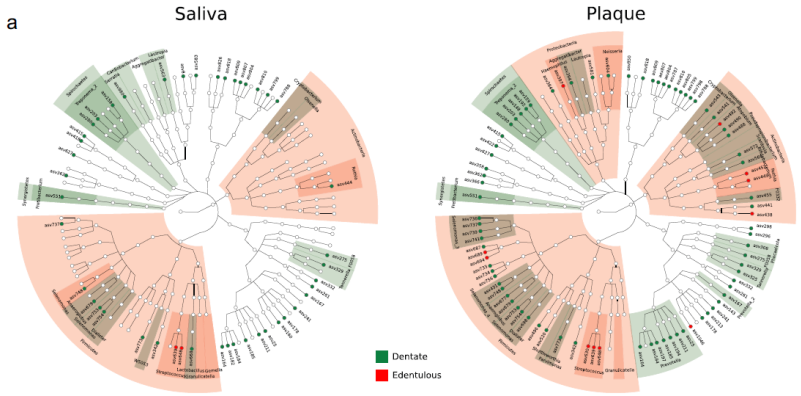
Xinyi L. Front Microbiol 2022

Maintaining oral health for a hundred years and more? - An analysis of microbial and salivary factors in a cohort of centenarians

2022

Caroline Sekundo, Eva Langowski, Diana Wolff, Sébastien Boutin & Cornelia Frese


## Plaque and salivary samples collected from 54 centenarians




**The structure and function of oral cavity and teeth as well as salivary secretion is influenced by and may influence the oral microbiome**

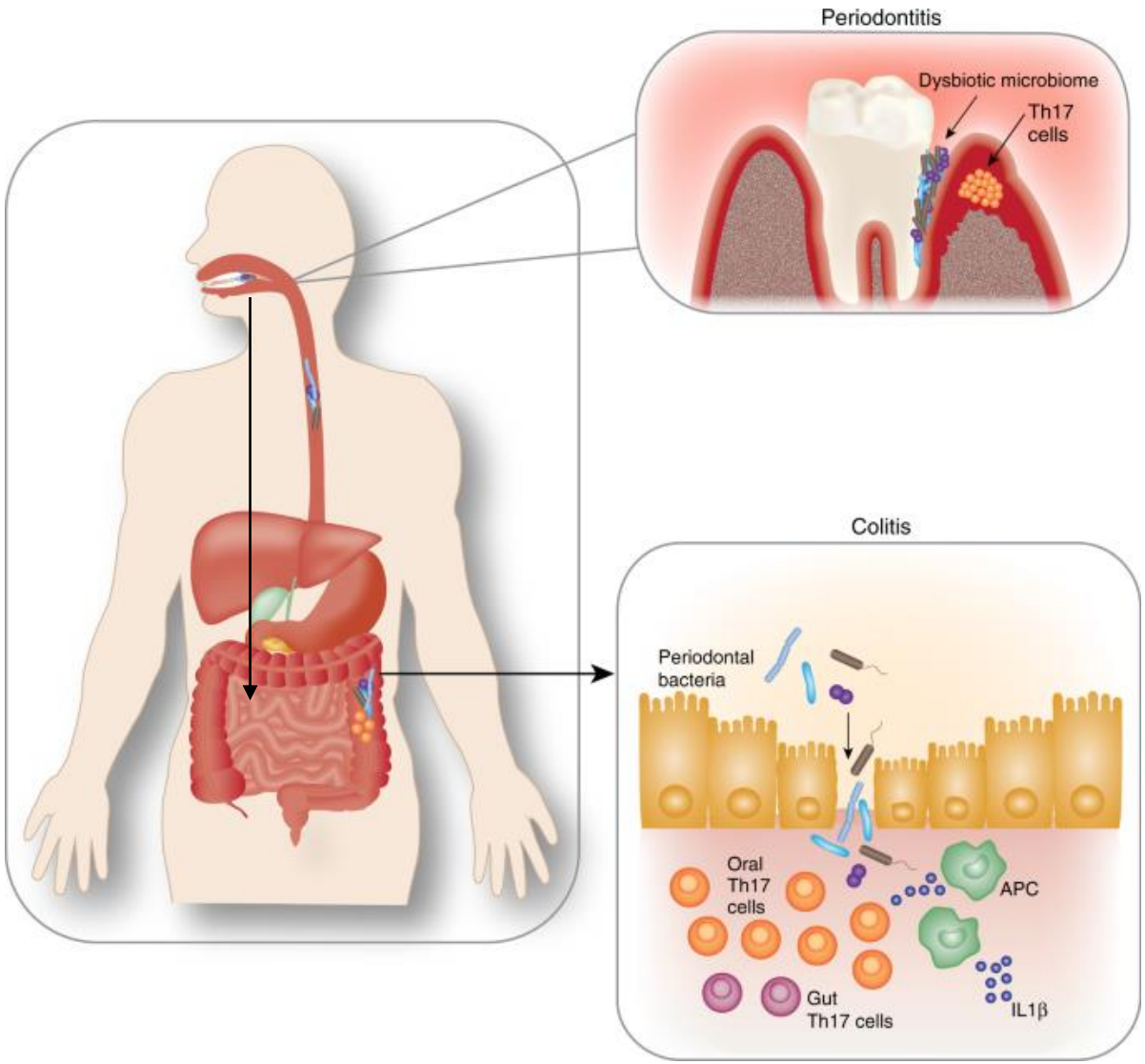
Table 2. Influence of clinical parameters on the microbiome structure and variance (PERMANOVA).

| | Saliva | | Plaque | |
|---|---|---|---|---|
| Parameter | $R^2$ | p-value | $R^2$ | p-value |
| Dentate | **0.07** | **<0.001** | **0.14** | **<0.001** |
| DMFT | **0.04** | **0.028** | **0.05** | **<0.001** |
| Capability of oral hygiene [48] | 0.02 | 0.451 | 0.02 | 0.604 |
| Frequency of tooth/ denture brushing | 0.01 | 0.843 | 0.01 | 0.89 |
| Frequency of dental visits | **0.03** | **0.038** | **0.04** | **0.015** |
| Dental service utilization | **0.03** | **0.044** | 0.03 | 0.053 |
| Residence | 0.03 | 0.154 | 0.02 | 0.299 |
| Disability | 0.02 | 0.333 | 0.02 | 0.205 |
| Degree of disability | 0.02 | 0.263 | 0.02 | 0.207 |
| Nursing care | 0.01 | 0.853 | 0.01 | 0.925 |
| Degree of nursing care | 0.03 | 0.131 | 0.02 | 0.635 |
| Sex | 0.02 | 0.477 | **0.03** | **0.01** |
| Age | 0.02 | 0.329 | 0.02 | 0.251 |
| Educational level | 0.02 | 0.353 | 0.02 | 0.209 |

# Oral microbiota dropping may inluence Gut Microbiota

**Oral Frailty**

**Dysbiosis**

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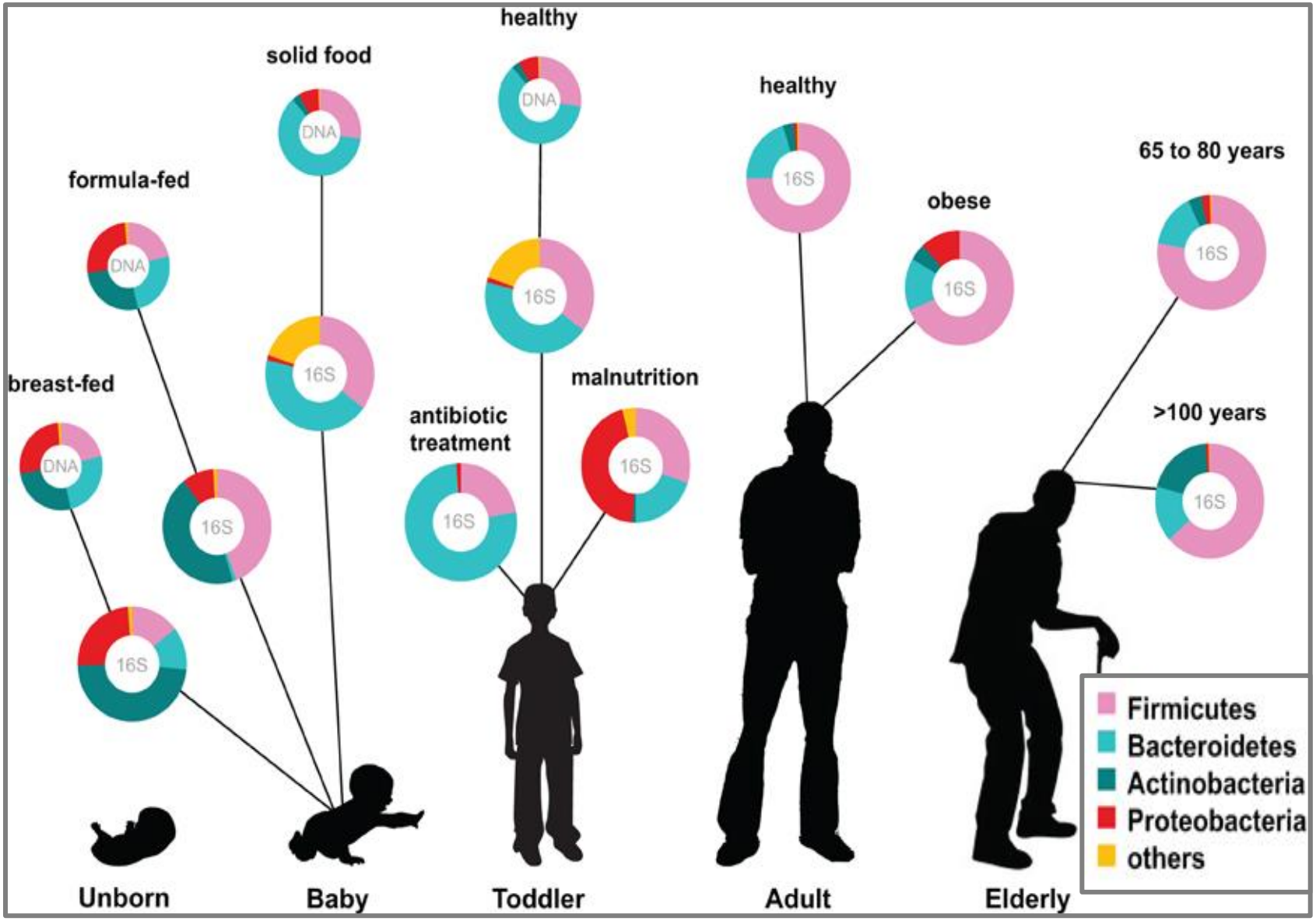
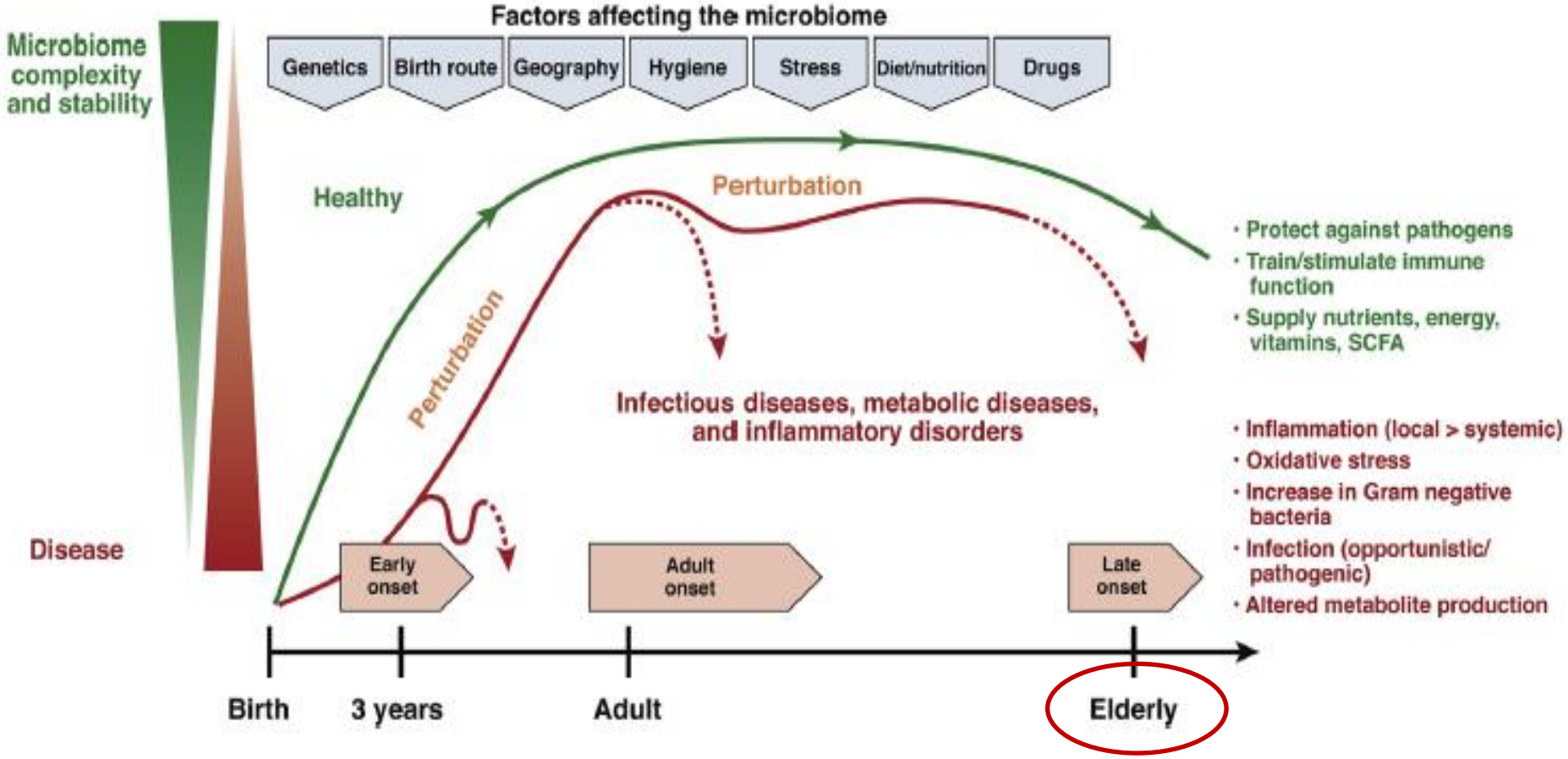
SCUOLA DI MEDICINA E CHIRURGIA
UNIVERSITÀ DEGLI STUDI DI NAPOLI
FEDERICO II

# Gut Microbiota and Aging



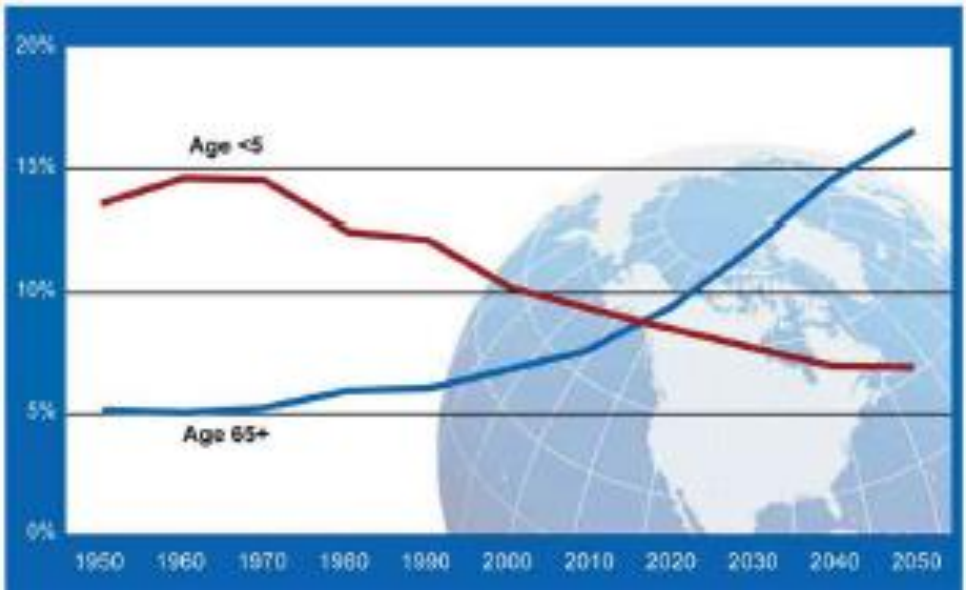
# Gut Microbiota Pertubation




Kostic AD et al, Gastroenterology 2014

World Health Organization

Life expectancy is growing: 1.5 years every 10 years




In 2050

1/5 people will be aged > 60 years

Triplet the number of > 80 years

more than 434 million *individuals*

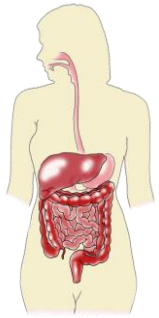
In 2060 life expectancy

82.5 years ♂

84.6 years ♀

Aging is the most important topic to be addressed


# Gastrointestinal tract and Aging



**ESOPHAGUS:**
↓ peristalsis LES function
Dysphagia, regurgitation, heartburn

**STOMACH:**
↓ gastric distension and emptying
↓ acid secretion, neuron function
delayed digestion, nausea and vomiting

**ILEUM:**
↓ motility, cellular turnover, secretion
bloating, pain, SIBO, malnutrition

**COLON:**
↓ myenteric neurons, muscle fibers,
↓ Calcium influx colonic transit time
constipation, diarrhea, incontinence

- ✓ Diabetes Mellitus
  may reduce gastric emptying
- ✓ Depression
  prolongs gut transit time
- ✓ Hypothyroidism
  prolongs oro-caecal transit time
- ✓ Kidney failure
  affects gastric emptying
- ✓ Drugs,
  anticholinergics, antidepressants, analgesics, Ca antagonist, affect gastrointestinal motility.

Hall KE, . 2005;
Petruzziello 2006

# Nutrition and Aging

The old subjects deeply change dietary habit due to

- Poor dentition
- Loss of taste and olfaction
- Gastrointestinal disorders
- Anorexia related to neuroendocrine changes
- Depression
- Decreased appetite
- Ability to obtain food


**Therefore, …**

Hall KE, et al. *Gastroenterology.* 2005;129:1305-1338.

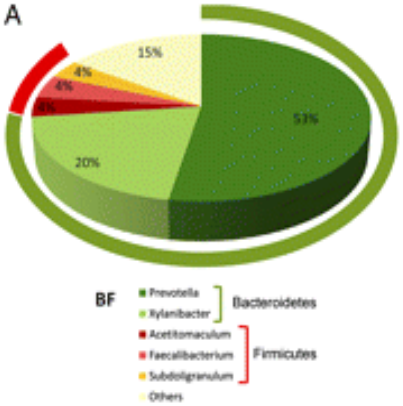
# Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

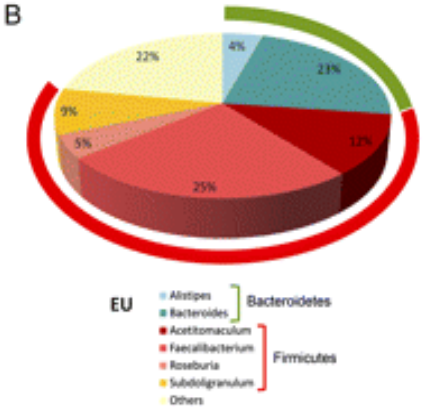
Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

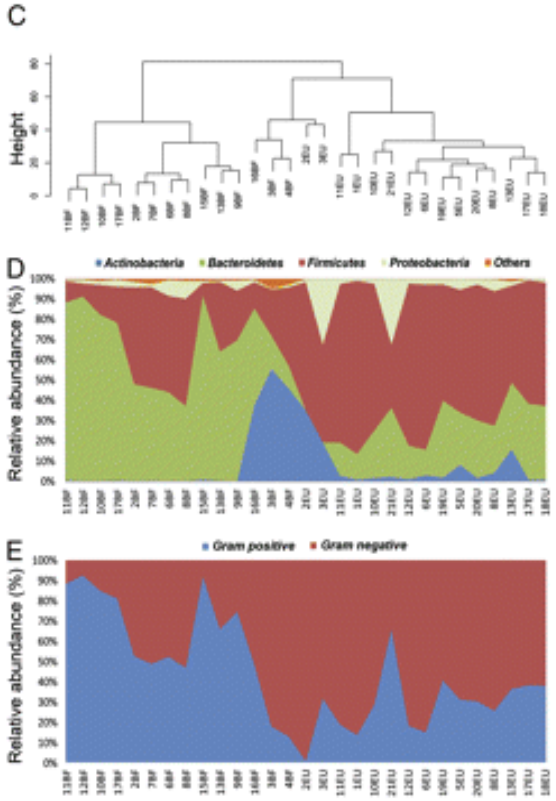

2010

African
Rural diet

European
Western diet




Rural Diet = ↑ vegetable fibre: ↑ Bacteroidetes ↑ Prevotella

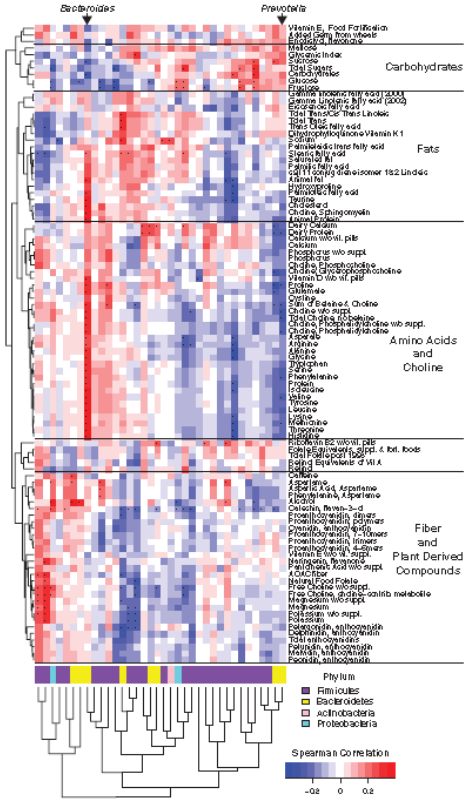
Western diet = ↑ starch and protein: ↑ Firmicutes, ↑ Proteobacteria

Science AAAS

2011

# Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes

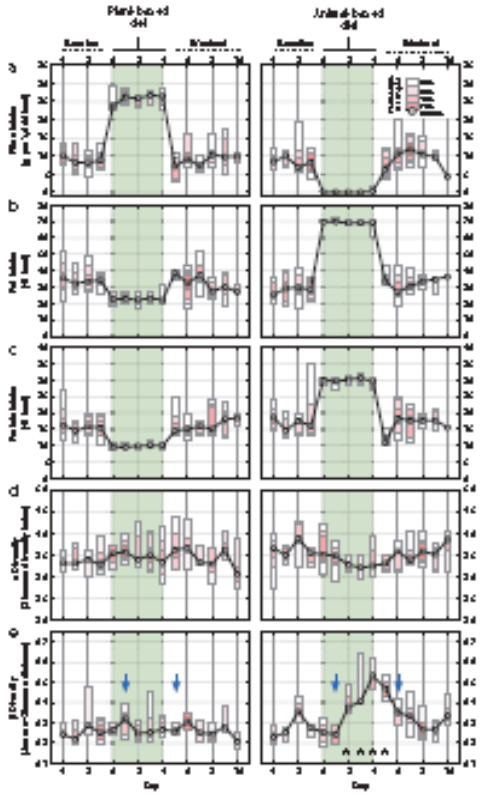
Gary D. Wu




LETTER nature 2014

# Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David



Diet modifies gut microbiota and is associated with specific enterotypes :

Protein-and animal fat — Bacteroides

Carbohydrates — Prevotella

Animal-fat diet is characterized by

↑↑ Alistipes, Bilophila and Bacteroides

↓↓ Firmicutes Eubacterium rectale Ruminococcus Roseburia,

# COMPLEXITY OF AGING PHENOTYPE

Age-induced changes in lifestyle and dietary habit

Age-induced changes in gut physiology and functionality

**CHANGE IN GUT MICROBIOTA**

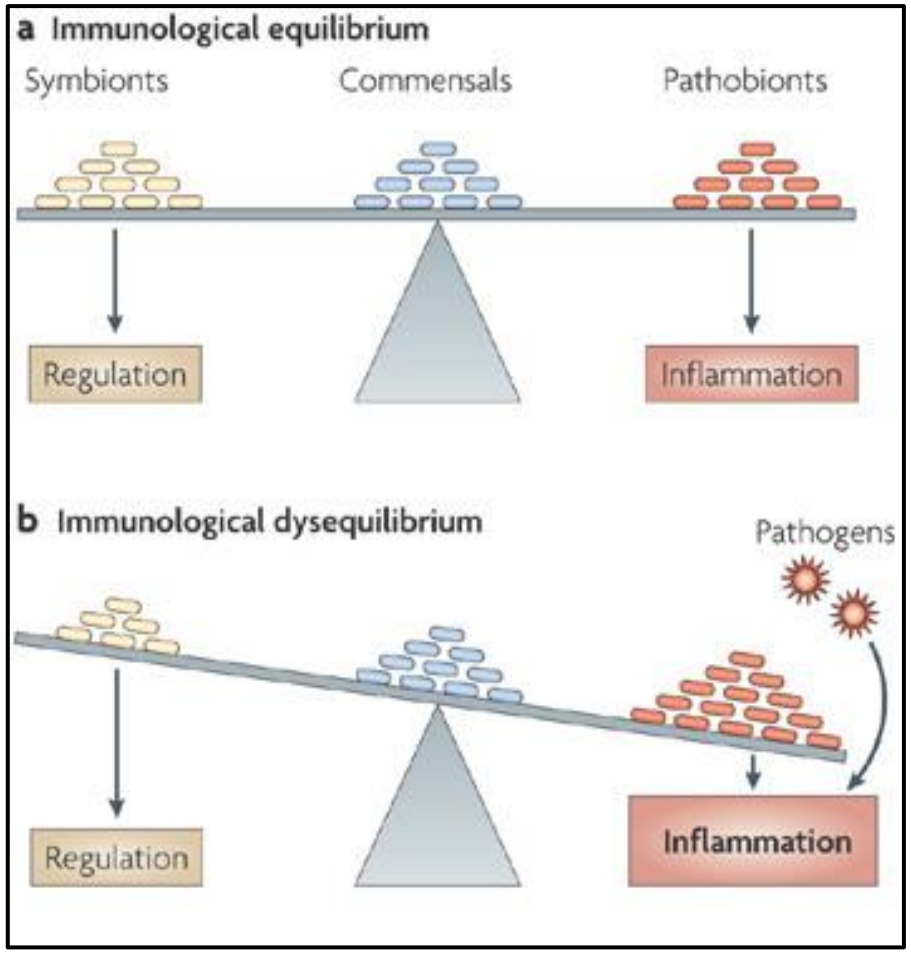
**Inflamm-Aging**

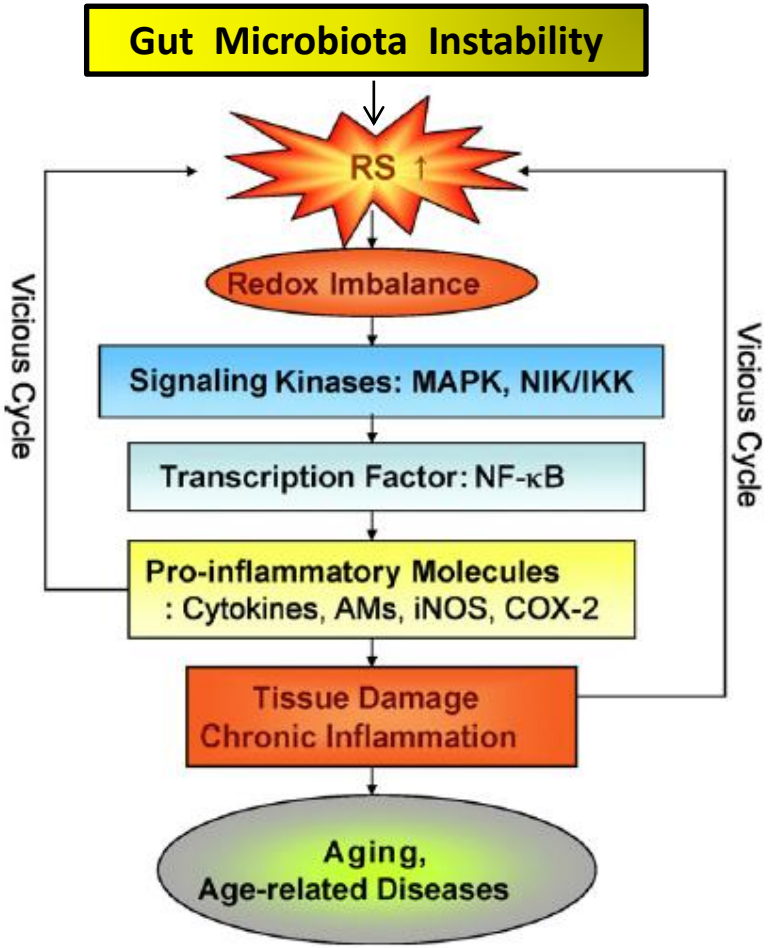
**Immuno-Senescence**

**Metabolic Disorders**

E. Biagi

# INFLAMM-AGING
## the low-grade chronic inflammatory status of the ageing process.



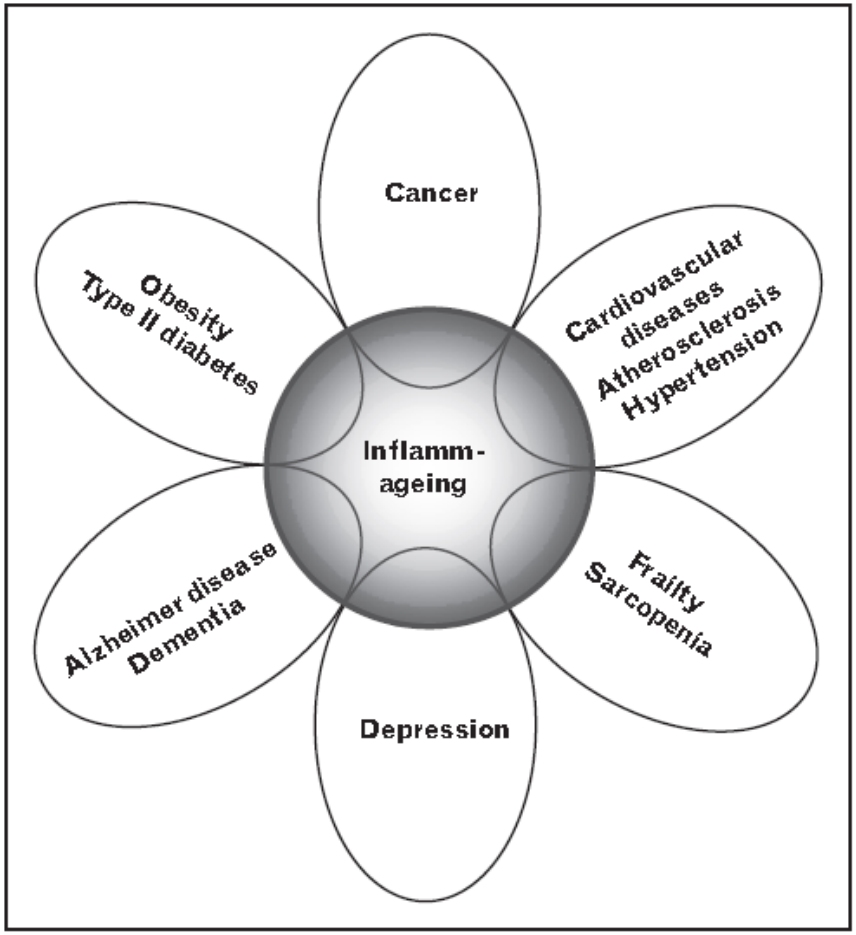

The mediators of inflammatory response (IL-1b, IL-6,TNF-a, COX-2, iNOS) are up-regulated during the aging process.

Chung H 2009

# INFLAMM - AGING

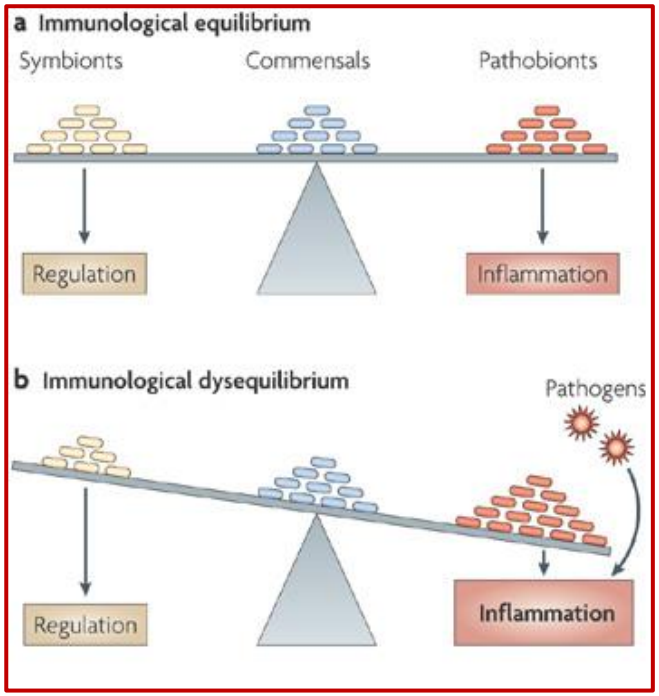
Intestinal inflamm-aging could be **the cause** of the increased prevalence of a clustering of metabolic abnormalities such as

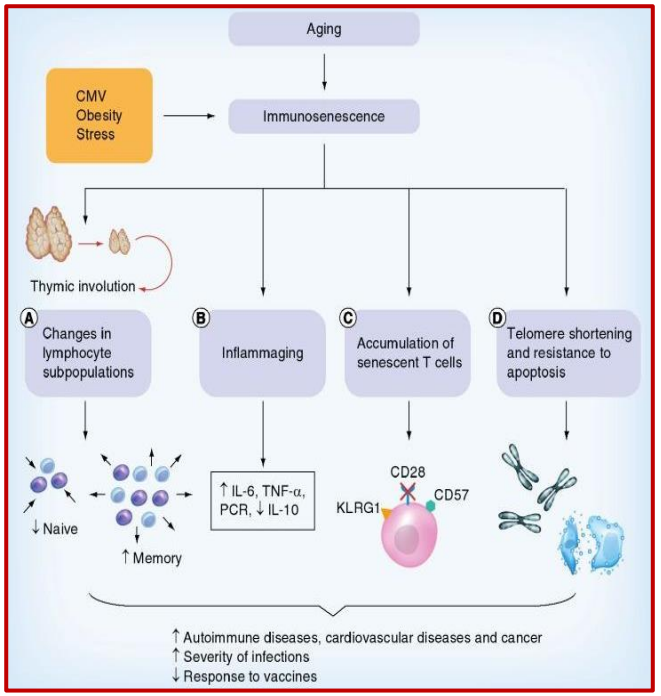
- **Obesity**
- **Dyslipidemia**
- **Hypertension**
- **Insulin resistance**
- **Diabetes type 2**
- **CANCER**




Gut microbiota contribute to fuel and maintain inflamm-aging at both local and systemic levels

# Inflamm-Aging & Immuno-Senescence




**Inflamm-Aging:** a low-grade chronic systemic inflammation established during physiological aging as the result of an imbalance between symbiotic and pathogen bacteria

**Immuno-Senescence:** a gradual decline of the function of the immune system due to the continuous exposure to a variety of antigens such as **bacteria** and toxic agents

# Immuno - Senescence

GI tract is the biggest immunologic organ

GALT = 70% of the body lymphocytes

Gut Microbiota constantly crosstalks with Immune system and, controls

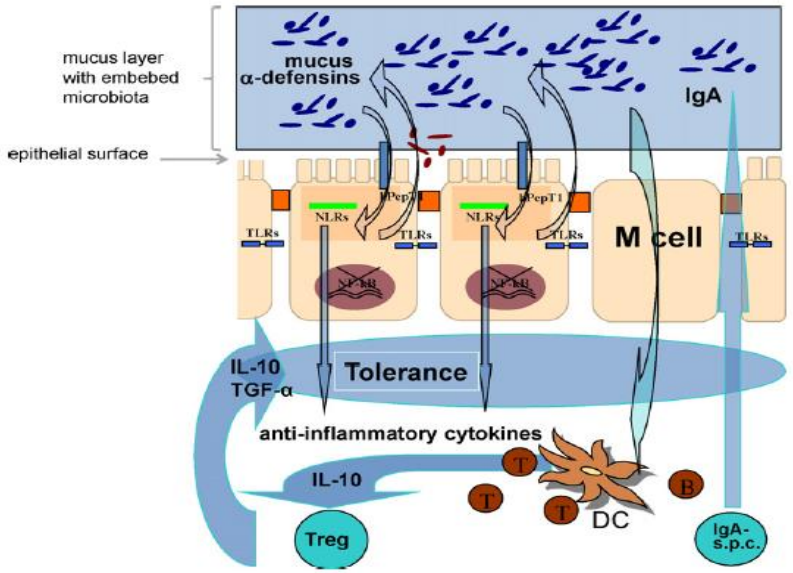
## *Innate mucosal immunity*

- *Defensins, lysozyme*
- *Toll Like Receptor*
- *s-IgA*
- *bactericidal proteins*

## *Acquired mucosal immunity*

- *MHC class II molecules*
- *T cells and B cells*
- *cytokines (IL1, TNFa, IL6)*
- *iNOS*

Older people suffer from a decline in Innate and Acquired immune system:




↓ M cells function (phagocytose microbes)
↓ Dentritic cells (antigen presentation)
↓ IgA production, function and transport
↓ T Cells and B cells failure

↓ tolerance to ingested nutrients
↑ susceptibility to infections

OPEN ACCESS Freely available online PLoS one

# Through Ageing, and Beyond: Gut Microbiota and Inflammatory Status in Seniors and Centenarians

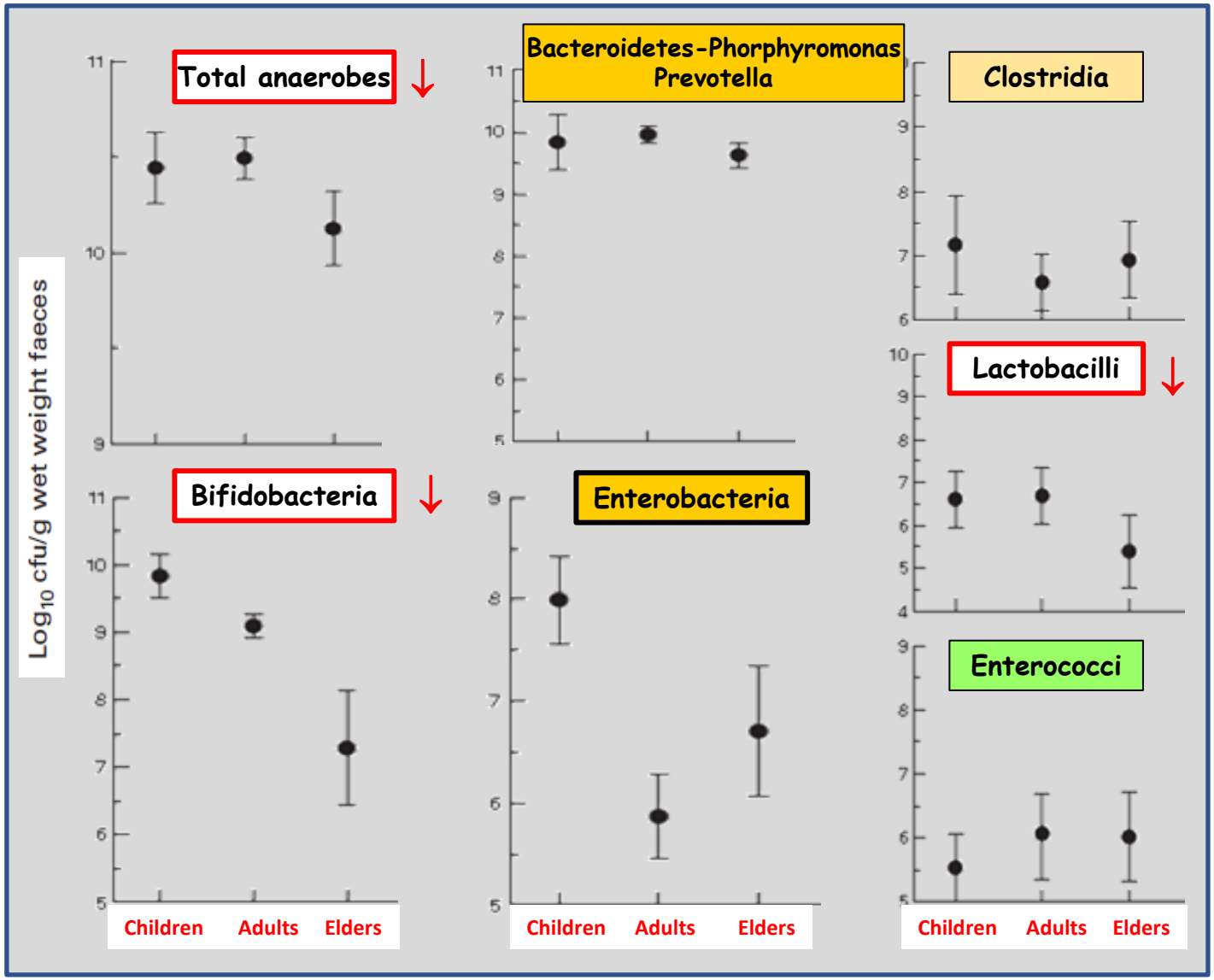
| | | |
|---|---|---|
| **C: CENTENARIANS** | **99-104 years** | **n. 21** |
| **E: ELDERLY** | **63 - 76 years** | **n. 22** |
| **Y: YOUNG** | **25 - 40 years** | **n. 20** |

## Lymphocyte subsets involved in immunosenescence

| | | Mean (%)± S.E.M[A] | | | P value[B] | | |
|---|---|---|---|---|---|---|---|
| **Lymphocyte subsets** | | **C** | **E** | **Y** | **C vs E** | **E vs Y** | **C vs Y** |
| Naïve T lymphocytes (CD45RA+CCR7+) | T helper | 15.3±2.5 | 22.5±1.3 | 33.1±2.0 | 0.008 | <0.0001 | <0.0001 |
| | T cytotoxic | 12.9±1.4 | 15.7±1.2 | 33.9±2.3 | | <0.0001 | <0.0001 |
| Central Memory T lymphocytes (CD45RA-CCR7+) | T helper | 34.8±3.5 | 21.5±1.9 | 13.7±1.1 | <0.001 | 0.009 | <0.0001 |
| | T cytotoxic | 11.4±1.2 | 9.8±1.5 | 5.0±0.6 | | 0.03 | <0.0001 |
| Effector Memory T lymphocytes (CD45RA-CCR7-) | T helper | 42.2±2.8 | 40.8±1.7 | 37.8±2.2 | | | |
| | T cytotoxic | 47.3±3.5 | 42.5±2.0 | 33.4±2.3 | | 0.007 | 0.002 |
| Terminal Effector T lymphocytes (CD45RA+CCR7-) | T helper | 7.6±1.1 | 15.2±1.6 | 15.4±0.7 | 0.03 | | <0.0001 |
| | T cytotoxic | 28.5±3.9 | 32.0±2.6 | 27.7±2.2 | | | |
| Effector T lymphocytes (CD28−) | T helper | 10.7±2.0 | 9.5±1.6 | 3.5±1.2 | | <0.001 | 0.001 |
| | T cytotoxic | 48.2±5.4 | 49.8±3.7 | 28.6±4.4 | | 0.002 | 0.02 |
| Activated T lymphocytes (CD25+) | T helper | 26.6±2.6 | 23.8±1.5 | 29.2±1.8 | | 0.03 | |
| | T cytotoxic | 13.3±2.9 | 6.6±0.7 | 5.5±0.4 | 0.003 | | 0.001 |

Biagi E 2010

# Age and disease related changes in intestinal bacterial populations assessed by cell culture, 16S rRNA abundance, and community cellular fatty acid profiles




**ELDERLY**
**vs**
**CHILDREN & YOUNG**

**Children n. 10**
**Adults n. 7**
**Elders n. 5**

**Decrease of**

- Total Anaerobes
- Bifidobacteria
- Lactobacilli

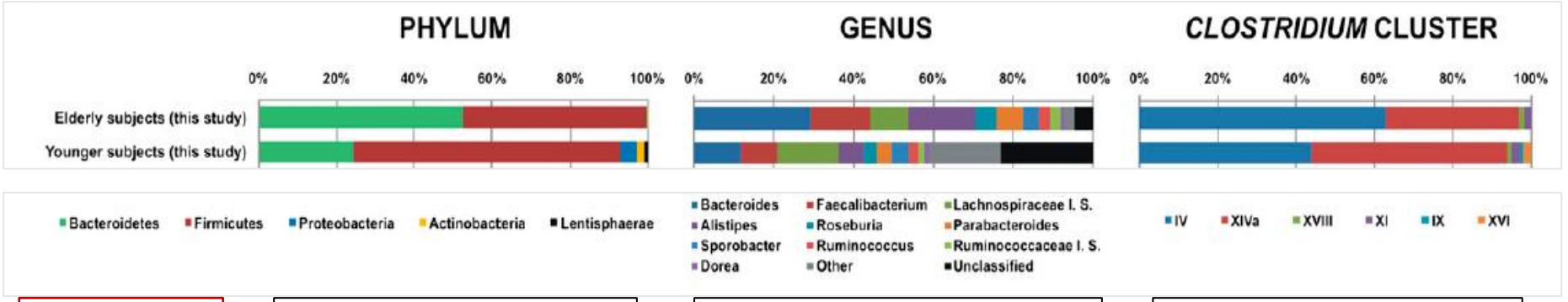
Hopkins Gut 2001

PNAS

# Composition, variability, and temporal stability of the intestinal microbiota of the elderly

Claesson MJ, 2011

## ELDERMET Consortium
## 161 subjects old (> 65 y) versus 9 young (< 65 y)




**Old vs Young**

↑ Bacteroidetes
↓ Firmicutes

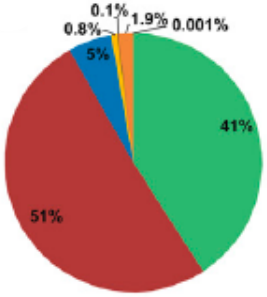
↓ Proteobacteria
↓ Actinobacteria
↓ Faecalibacteria

↑ Bacteroides,
↑ Alistipes
↑ Parabacteroides

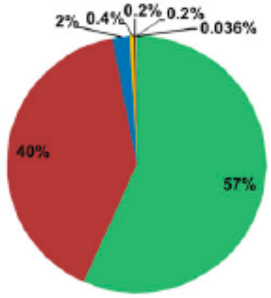
↑ Clostridium IV

Bacteroidetes

Firmicutes




**Young**




**Old**

**BMC Microbiology**

BioMed Central

Research article

Open Access

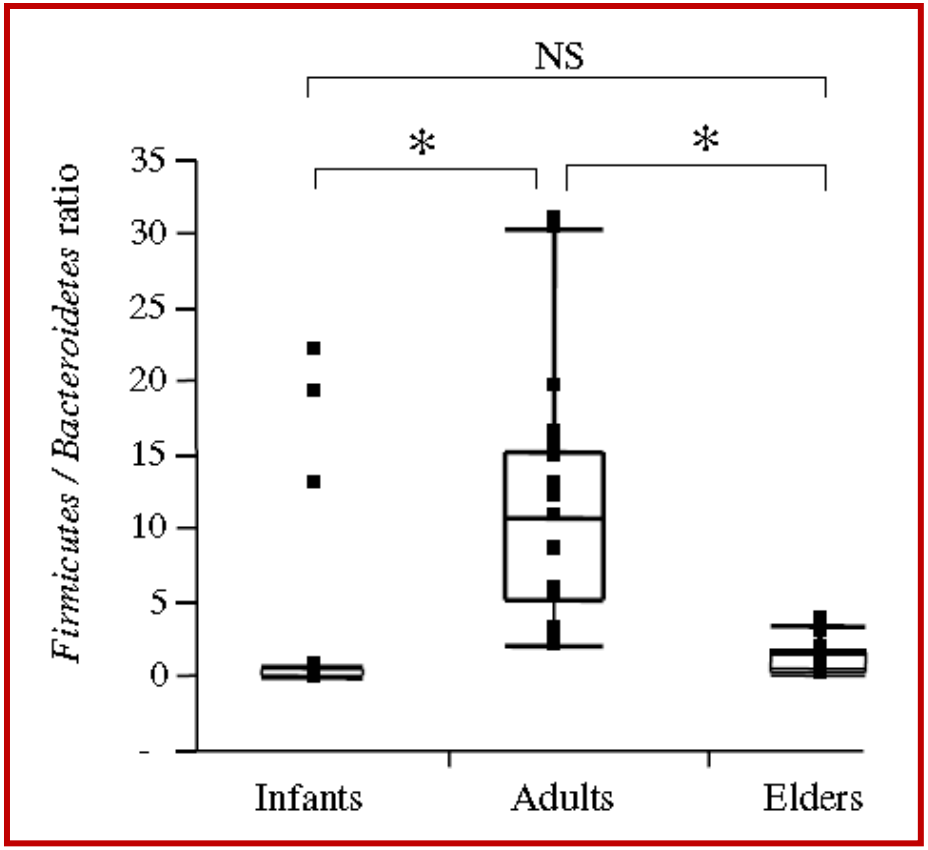
# The *Firmicutes/Bacteroidetes* ratio of the human microbiota

**21 Infants** **aged < 10 months**

**21 Adults** **aged 25-45 years**

**20 Elders** **aged 70-90 years**

*Firmicutes/Bacteroidetes ratio*
*evolves* during life stages
but,
no significant difference was found between infants and elders




Mariat D 2009

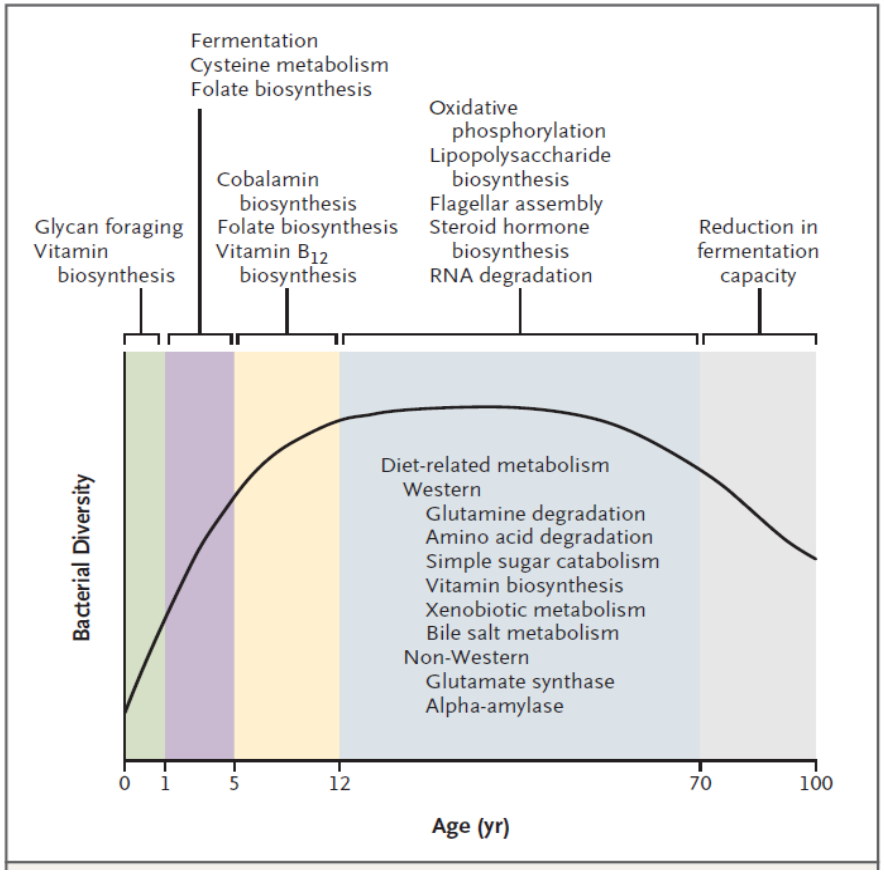
The NEW ENGLAND JOURNAL of MEDICINE

# The Human Intestinal Microbiome in Health and Disease

**2016**

Susan V. Lynch, Ph.D., and Oluf Pedersen, M.D., D.M.Sc.

Temporal development of the Gut microbiota in humans




In the elderly, the gut microbiota become compositionally unstable and less diverse, events that are associated with coexisting declines in immunocompetence

REVIEW ARTICLE

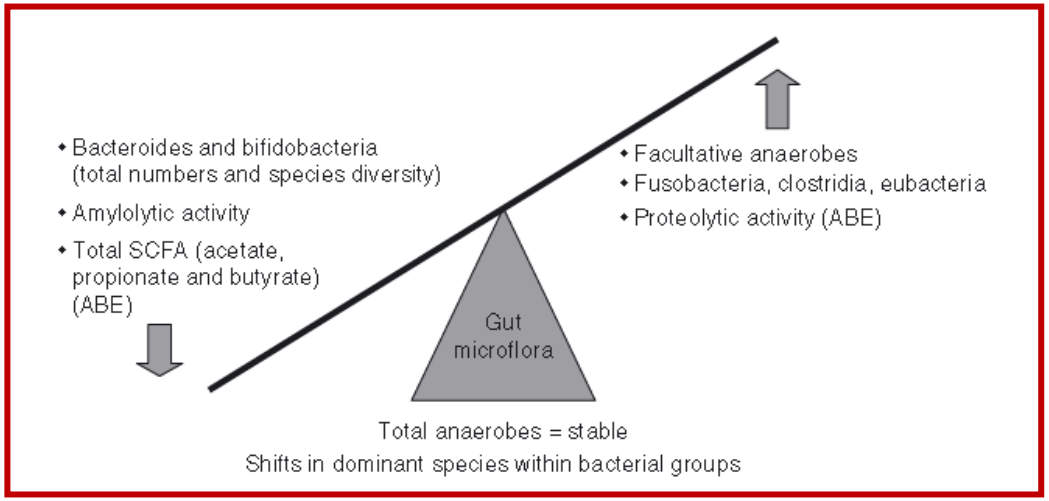
**Intestinal bacteria and ageing**

E.J. Woodmansey 2007

## Getting OLDER

↓ **Bifidobacteria**
↓ **Faecalibacterium P.**
↓ **Firmicutes (many species)**

↑ **E. coli**
↑ **Staphylococcus**
↑ **Proteobacteria (many species)**




In elderly there is a shifts in the composition of the gut microbiota and a general reduction in species diversity **"Microbiota Instability"**

# Fecal Microbiota Composition and Frailty

Sandra P. van Tongeren,[1] Joris P. J. Slaets,[2] H. J. M. Harmsen,[1] and Gialt W. Welling[1]*


## Fecal microbiota composition of elderly with different frailty score

| | Low-Frailty (n 10) | | High-Frailty (n 13) | |
|---|---|---|---|---|
| | number | percent | number | percent |
| Total Bacteria | 53.9 | 100 | 54.2 | 100 |
| Bacteroides -Prevotella | 11.0 | **24.2*** | 4.5 | **9.4*** |
| Ruminococcus | 6.3 | 15.2 | 12.7 | 23.8 |
| Fecalibacterium Prausnitzii | 1.2 | **3.1*** | 0.3 | 0.7 |
| ***Bifidobacterium*** | 0.9 | 1.3 | 0.2 | 0.5 |
| ***Lactobacillus*** | **0.1*** | **0.3*** | **0.03*** | **0.04*** |
| ***Enterobacteriaceae*** | **0.05*** | 0.1 | **0.3*** | 0.6 |

*p<0.05

In the elderly with high frailty scores

↓ Lactobacilli 26-folds
↓ Bacteroides-Prevotella 3-folds
↓ Faecalibacterium p. 4-folds

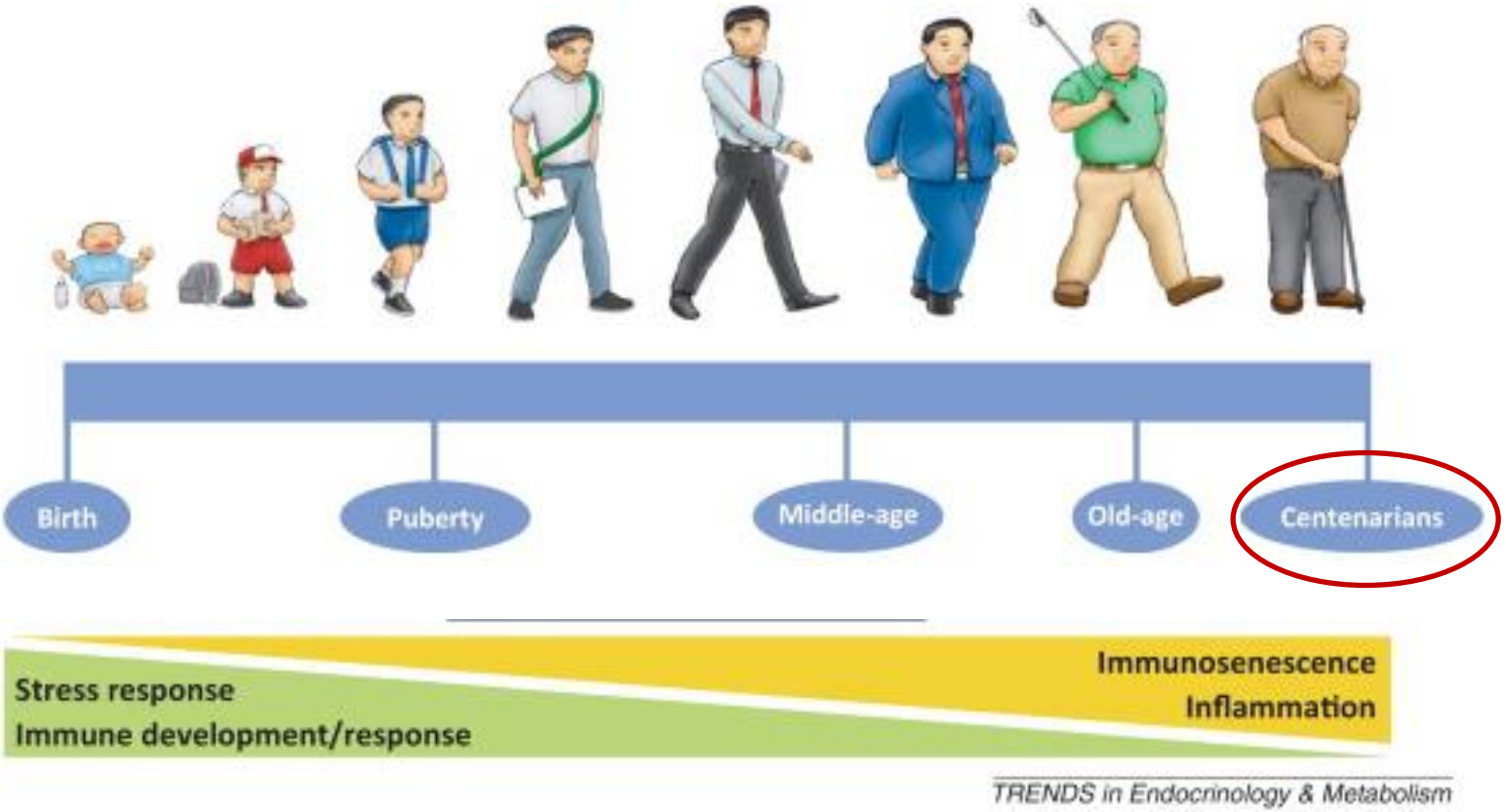
↑ **Enterobacteriaceae** 7-folds

Frailty and Hospitalization correlated

**Negatively** with
Lactobacilli, Fecalibacterium P.
Bacteroides/ Prevotella

**Positively** with
Enterobacteriaceae

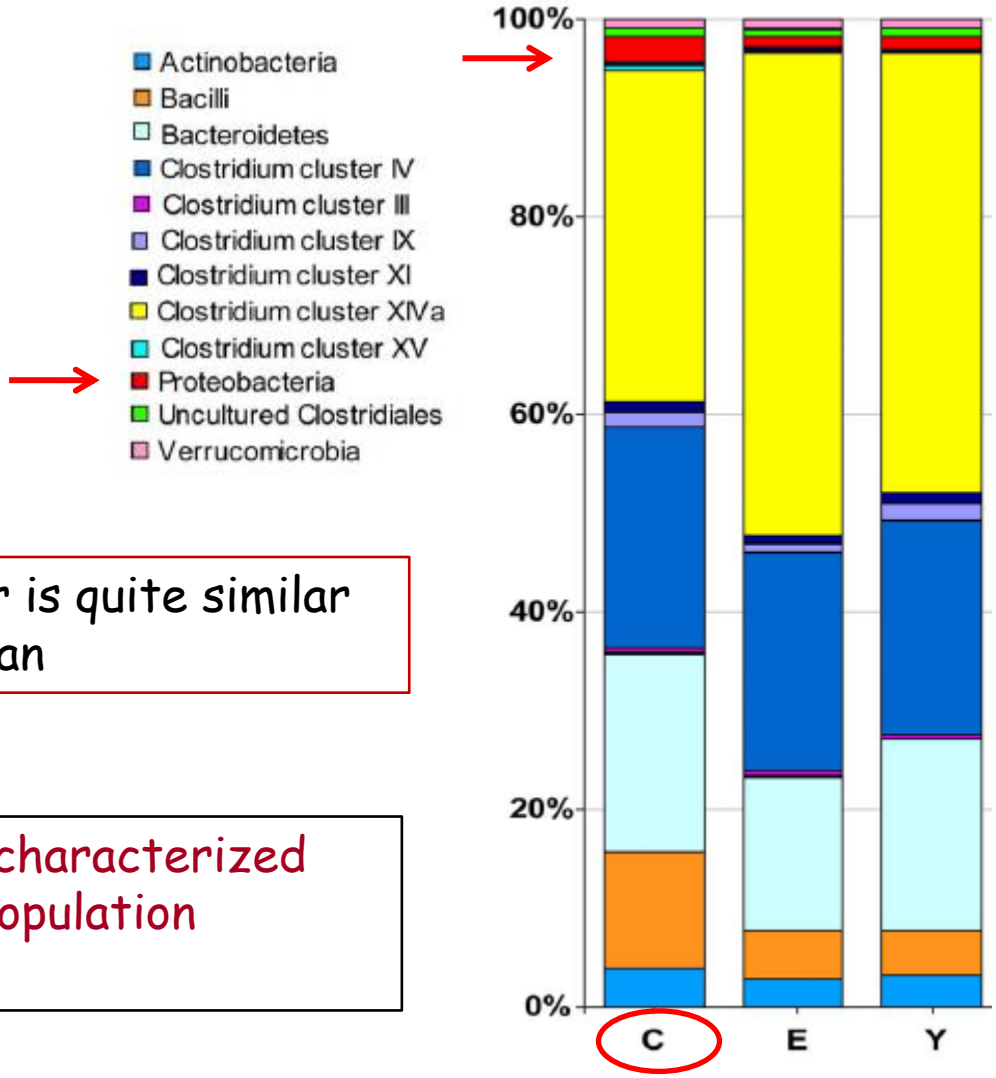
The microbiome has a reciprocal relationship with age,
**it changes as the host ages and is altered in age-related disease**,
but it also modifies age-related impairment of the host



OPEN ACCESS Freely available online PLoS one

# Through Ageing, and Beyond: Gut Microbiota and Inflammatory Status in Seniors and Centenarians

| | | |
|---|---|---|
| **C: CENTENARIANS** | **99-104 years** | **n. 21** |
| **E: ELDERS** | **63 - 76 years** | **n. 22** |
| **Y: YOUNG** | **25 - 40 years** | **n. 20** |




The Gut Microbiota of Young and Elder is quite similar but differs from that of the Centenarian

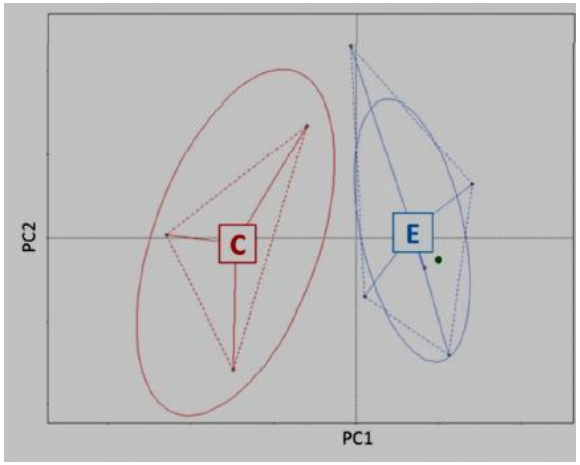
In centenarians, the Gut Microbiota is characterized by a rearrangement in the Firmicutes population and by an increase of Proteobacteria

Biagi E 2010

Research Paper

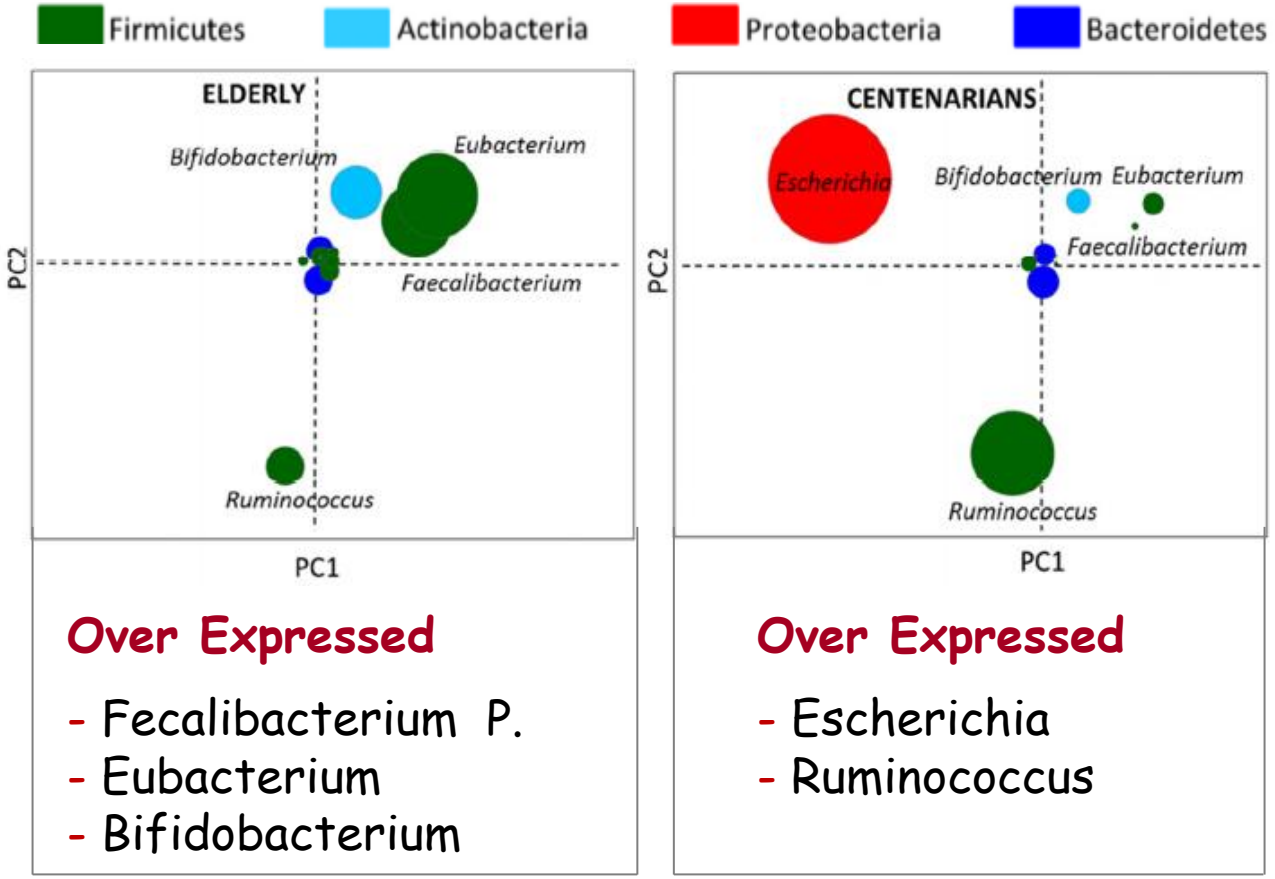
# Ageing process deeply affects the structure of the human gut microbiota

Elderly (63-76 yrs) n. 22  Centenarians (99-104 yrs) n. 21




**116 microbial genes**

**correlated with ageing at significant level**




**Over Expressed**

- Fecalibacterium P.
- Eubacterium
- Bifidobacterium

**Over Expressed**

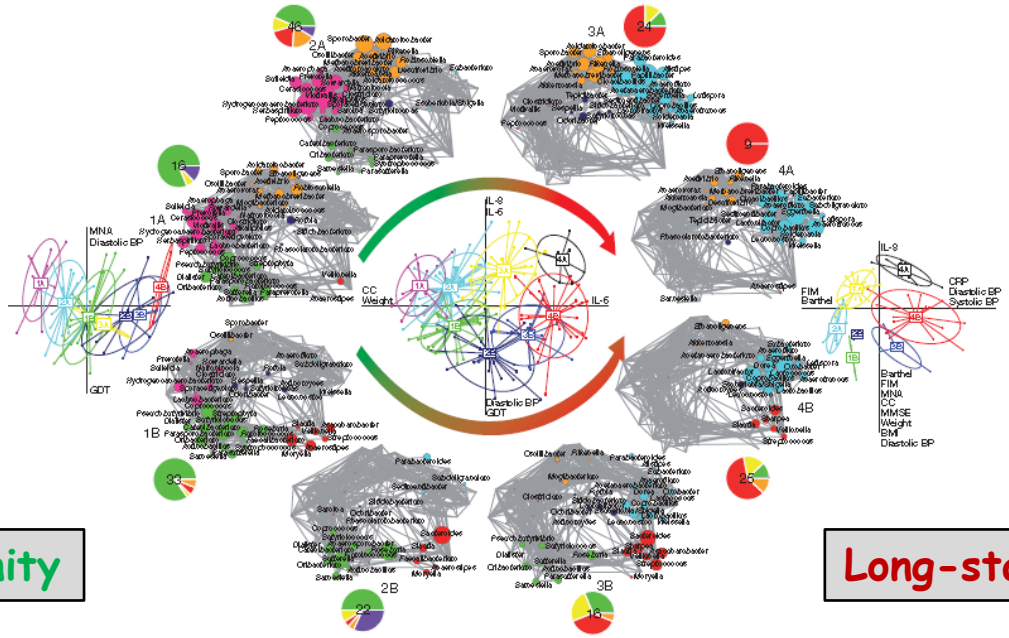
- Escherichia
- Ruminococcus

Rampelli et al, Aging 2013; 5(12): 902-12

# Gut microbiota composition correlates with diet and health in the elderly


178 old subjects aged, mean age 78±8 years, range 64-102 years

**Community dwelling** **Rehabilitation** **Long-stay**




**Community** **Long-stay**

**Faecal microbiota composition**

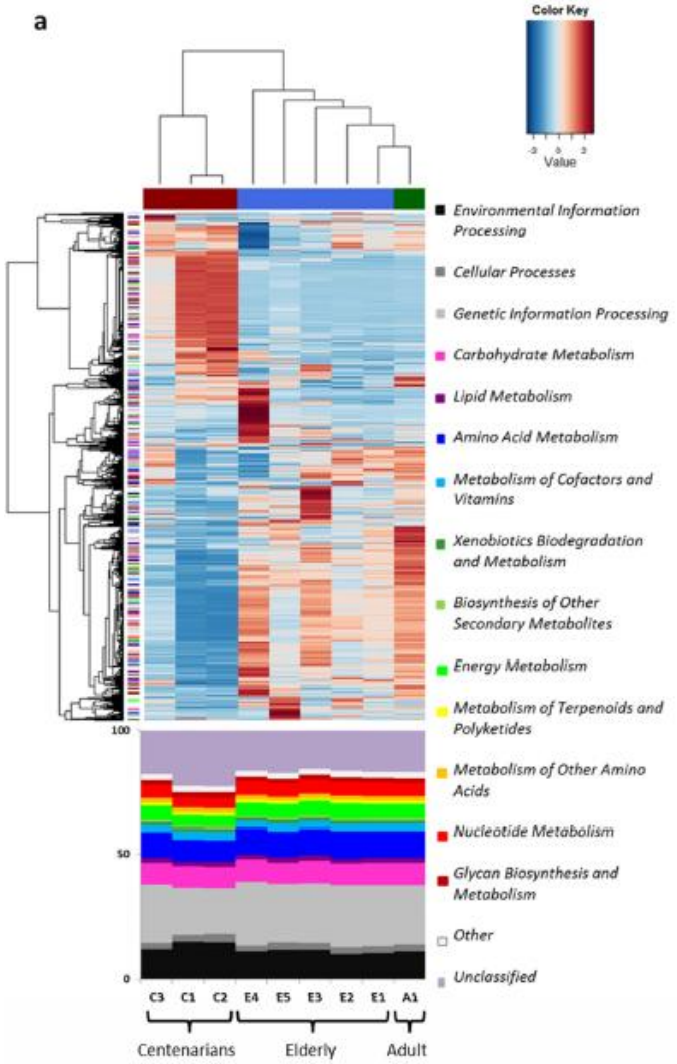
Microbiota analysis separated elderly subjects based upon where they live

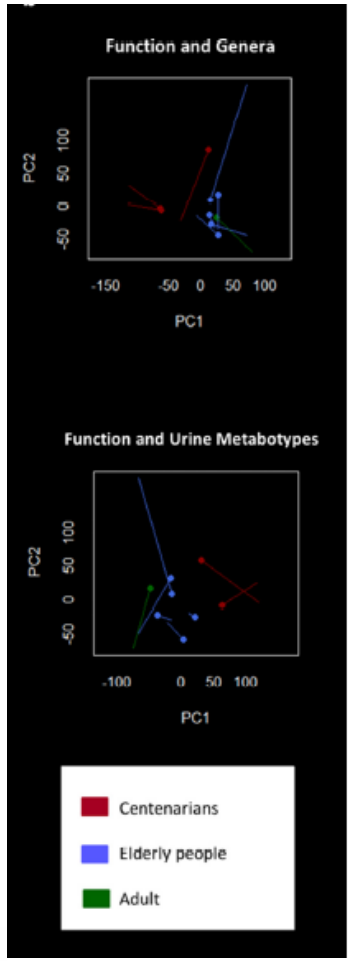
Claesson MJ, 2012

# Centenarians

↓ Firmicutes = ↓ genes involved in saccharolytic metabolism

↑ Proteobacteria ↑ genes involved in proteolytic metabolism



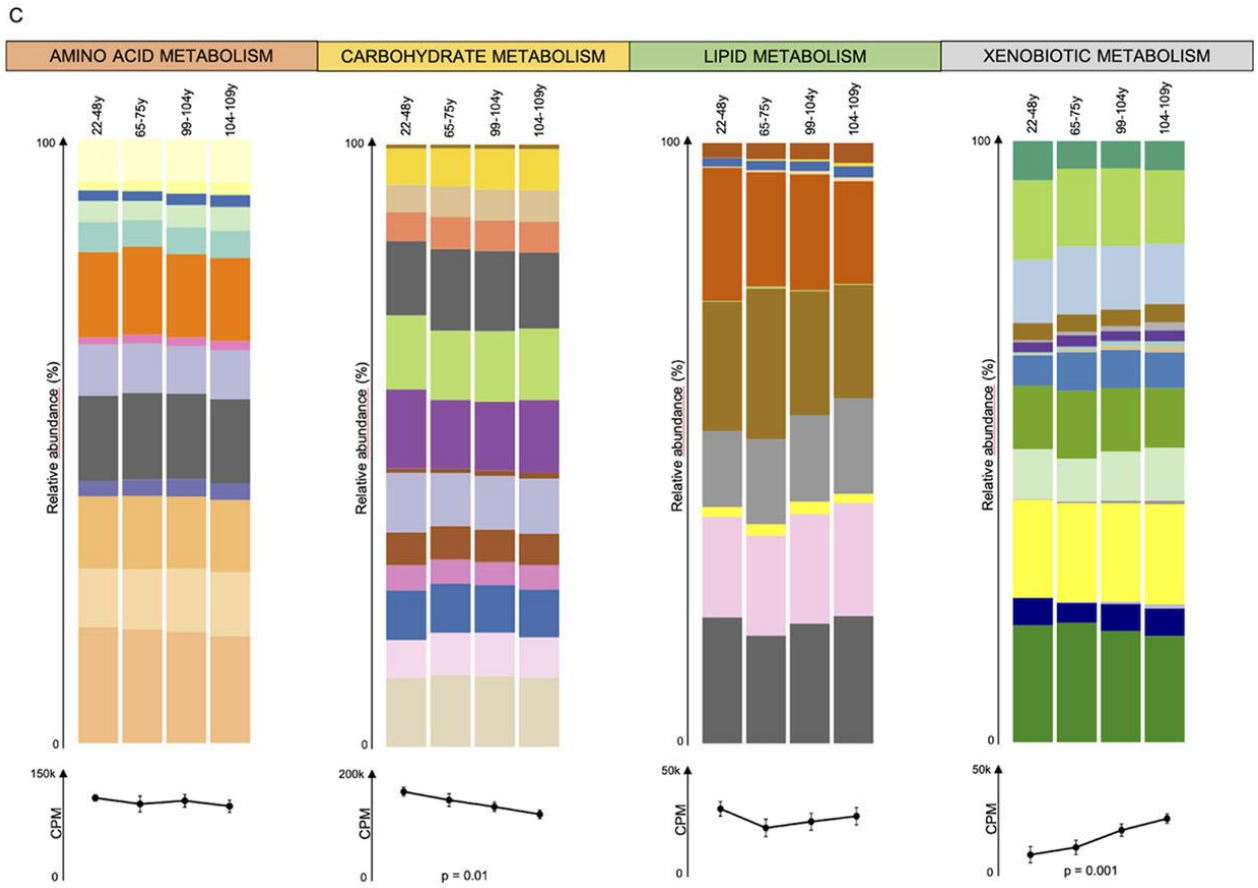

The Gut Microbiota of Centenarians is structurally and functionally compromised, changing from a saccharolytic to proteolytic metabolisms

Rampelli et al, 2013;

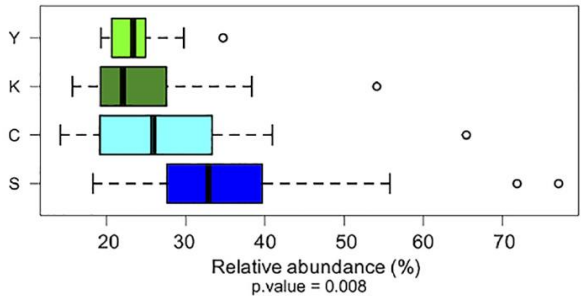
AMERICAN SOCIETY FOR MICROBIOLOGY

# Shotgun Metagenomics of Gut Microbiota in Humans with up to Extreme Longevity and the Increasing Role of Xenobiotic Degradation

mSystems®




11 young adults 22- 48 ys
13 younger elderly 65-75 ys
15 centenarians 99-104 ys
23 semi supercent. 105-109 ys

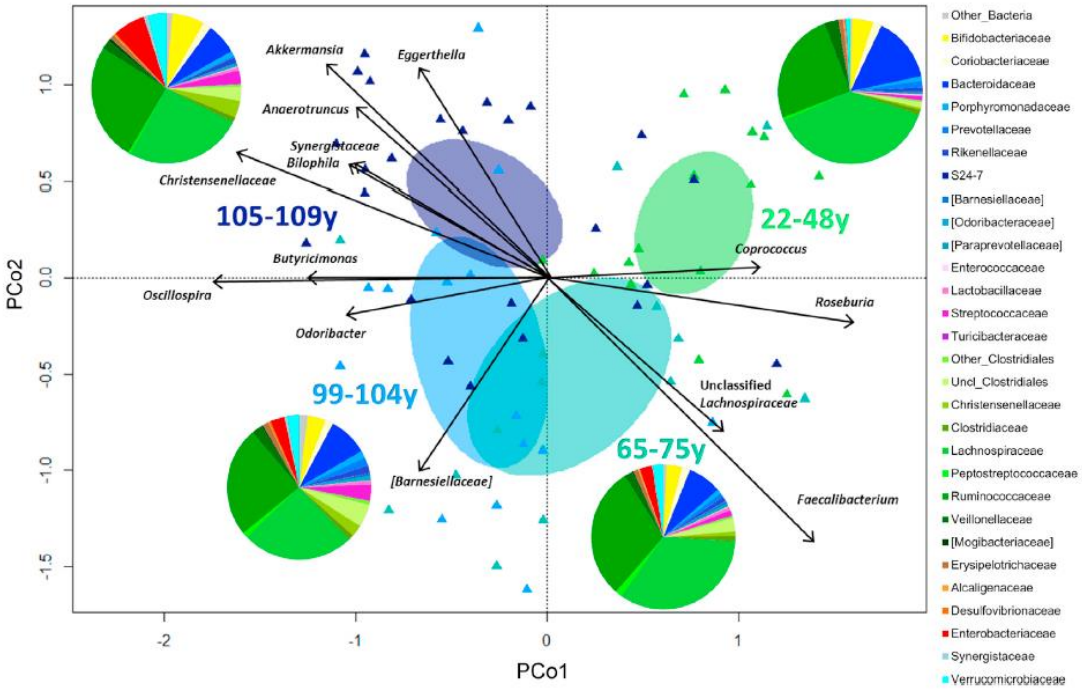



The gut microbiome of centenarians and semisupercentenarians is more suited for **xenobiotic degradation** and shows a **rearrangement in metabolic pathways** related to carbohydrate, amino acid, and lipid metabolism

S. Rampelli, 2020

Current Biology
Gut Microbiota and Extreme Longevity
Current Biology
Report
Biagi 2016

| | | |
|---|---|---|
| 24 | Semisupercent. | 105-109 y |
| 15 | Centenarians | 99–104 y |
| 15 | Elderly | 65–75 y |
| 15 | Adults | 22–48 y |




In longevity and extreme longevity, occurs changes that, even accommodating **opportunistic and allochthonous bacteria**, **might possibly support health maintenance** during aging, such as an enrichment and/or higher prevalence of **health associated groups (e.g., Akkermansia, Bifidobacterium, and Christensenellaceae).**

Correspondence

# Gut microbiota signatures of longevity

Current Biology
Magazine

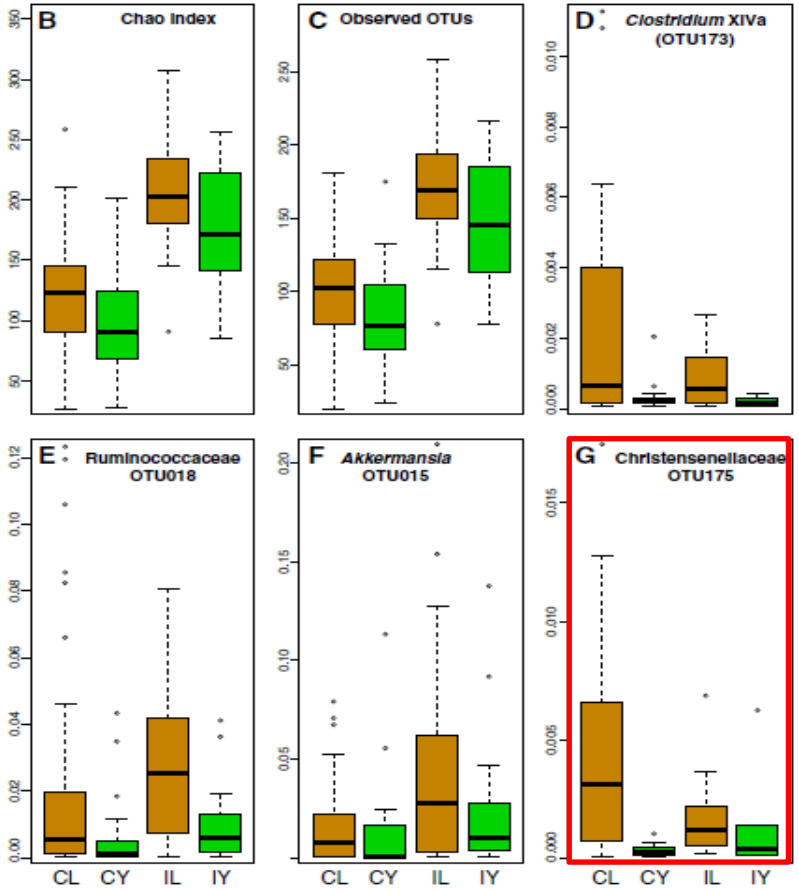
F. Kong 2016

**CL: Cinese Longeve**

**CY: Cinese Young**

**IL: Italian Longeve**

**IY: Italian Young**




## Christensenella

**Negative correlation with**

- BMI percentile Lim YM 2016
- Lipid traits Lopez-Contreas 2017

**Positive correlation with**

- SCFA Org E. 2019

**Christensenellaceae** can represent a signature of adaptation to the changes associated with the long living, regardless of lifestyle and dietary habits

**Christensenella:** a new candidate of the **Nextgeneration probiotics**

Current Biology
Gut Microbiota and Extreme Longevity
Current Biology Report
Biagi 2016

15 younger elderly 65–75 years
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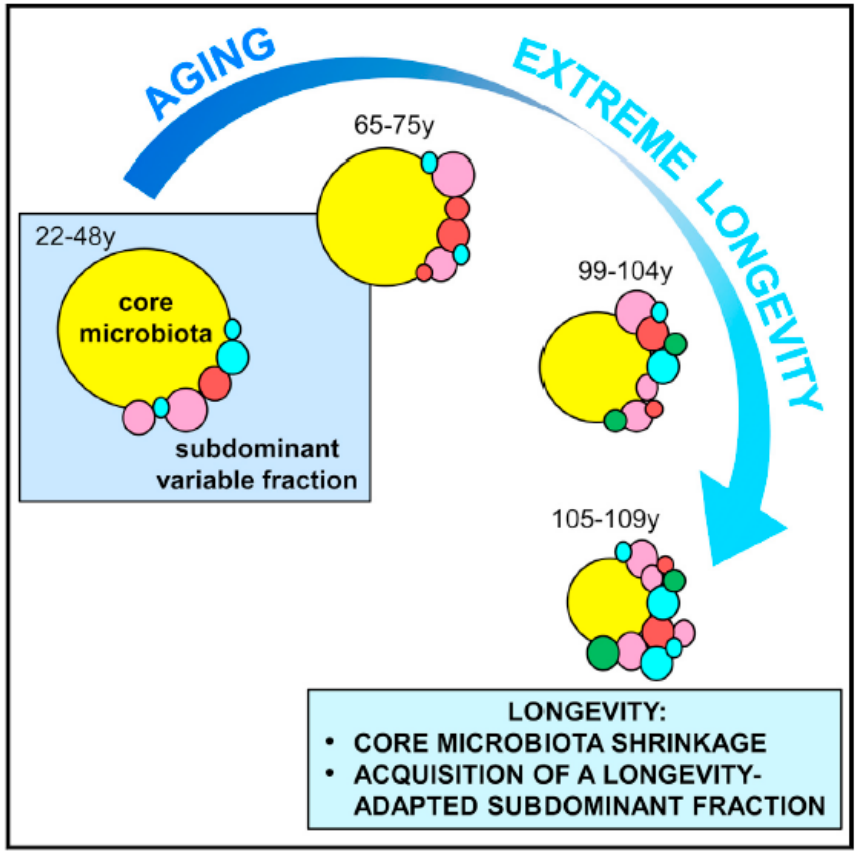


A core microbiota accompanies human life, decreasing in abundance along with aging

In longevity, the age-related enrichment of subdominant taxa is boosted

The microbiota of longevous hosts accommodates **allochthonous bacteria**

‘‘Longevity adaptation’’ seems to involve **enrichment in health-associated gut bacteria**

The gut microbiome has been proposed as a possible determinant of healthy aging

# Based on a detailed literature three kinds of taxonomic groups can be identified

**Group 1**: **taxa that are lost with ageing and especially during unhealthy ageing**
(such as *Prevotella*, *Faecalibacterium*, *Eubacterium rectale*, *Lachnospira*, *Coprococcus* and *Bifidobacterium*)

**Group 2: pathobionts that increase with ageing, especially in unhealthy ageing**
*Eggerthella*, *Desulfovibrio*, Enterobacteriaceae,*Clostridium* species, Ruminococcus torques, Fusobacteria, *Streptococcus* and Enterobacteriaceae

**Group 3: healthy ageing- associated taxonomic putatively beneficial** *Akkermansia*, Christensenellaceae, *Butyricimonas*, *Odoribacter* and *Butyricicoccus*).
They become more abundant with age but are lost during unhealthy ageing

*The role of the infinitely small in nature is infinitively great* (Louis Pasteur)