Exploring the Predisposition to Chronic Disease

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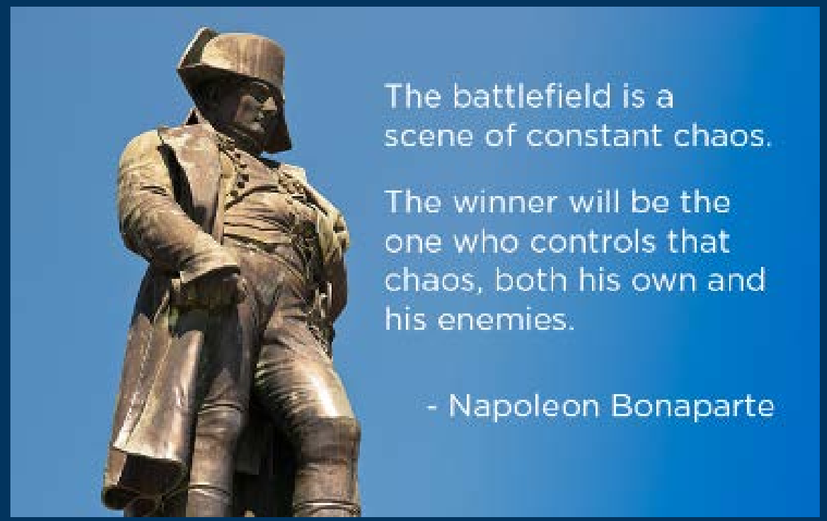
Chronic Disease:
We are not winning this war !

- Chronic diseases are responsible for 7 of 10 deaths each year
- Treating chronic diseases accounts for 86% of our nation's health care costs

- Why are we not winning
  - Healthy aging concepts not being followed
    - Food choices, exercise
  - Inflammatory states
    - Obesity
    - T2DM
    - Cancer
    - RA, IBD, etc etc



Diseases where Inflammation is thought to be part or all of the etiology of the disease !

- Diabetes
- Obesity
- Metabolic syndrome
- Heart disease
  - atherosclerosis
- Neuropsychiatric
  - Depression
  - Anorexia nervosa
  - Alzheimer’s
  - Parkinsons
- Hepatic diseases
  - NASH
  - cirrhosis
- Infectious disease
  - General, TB, Malaria
- Asthma
- Allergy
- Inflammatory Bowel Disease
- Autoimmune diseases
- Peptic ulcer disease
- HIV / AIDS
- Cancer
  - Metabolic effects (cachexia)
  - metastasis
- Critical Care / Surgery
  - Trauma
  - Pancreatitis
  - Transplantation
  - Sepsis
  - ARDS / ALI
- Hypoxia
- Aging
- etc etc etc

“Many types of injury produce a similar inflammation”

Hunter J (1794) A treatise on blood, inflammation and gunshot wounds

Common Chronic Conditions Seen In Clinical Practice Associated with Chronic Inflammation

- Aging and age-associated diseases
- Obesity and Metabolic Syndrome
- Diabetes
- Cardiovascular diseases
- Cancer
- Neuroinflammatory and neurocognitive conditions
- Digestive disorders including Inflammatory Bowel Disease (IBD)
- Autoimmune conditions
- Osteoarthritis and degenerative joint diseases

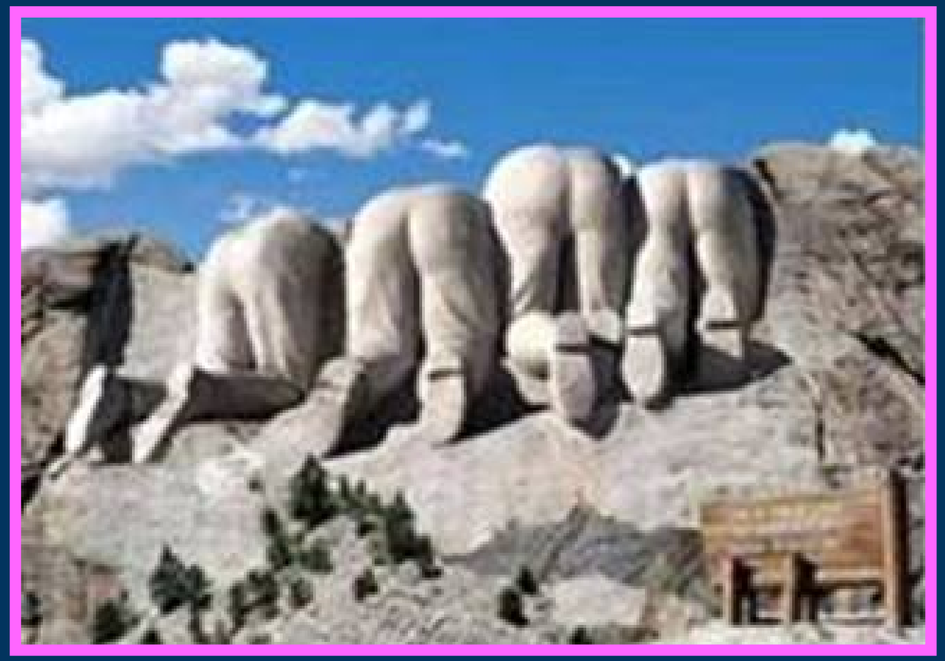
Ferguson LR et al Arch Tox 2017

Interpreting The Evidence: Different Perspectives May Result !

US Perspective

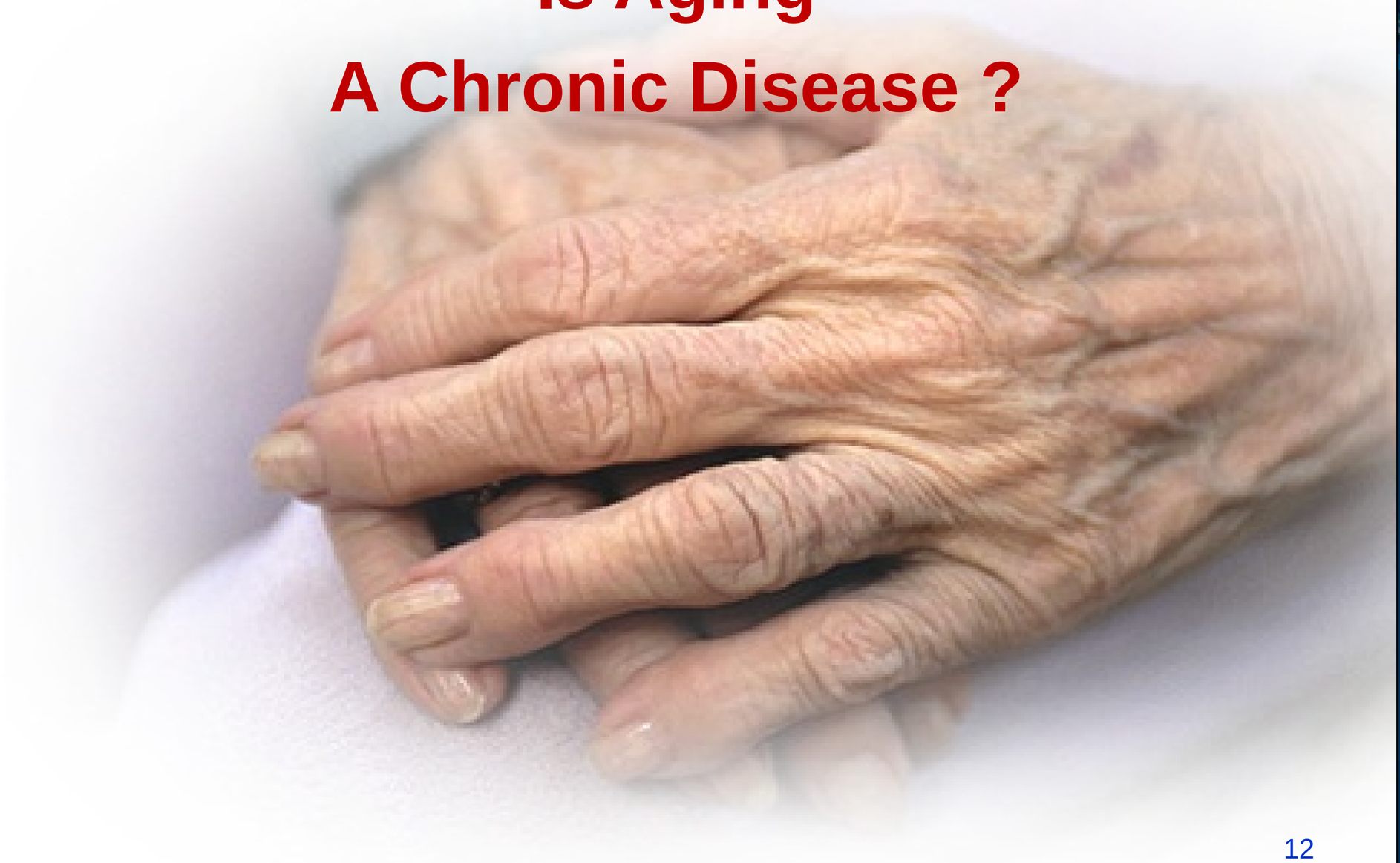
Interpreting Evidence:
Many Different Perspectives !

US Perspective

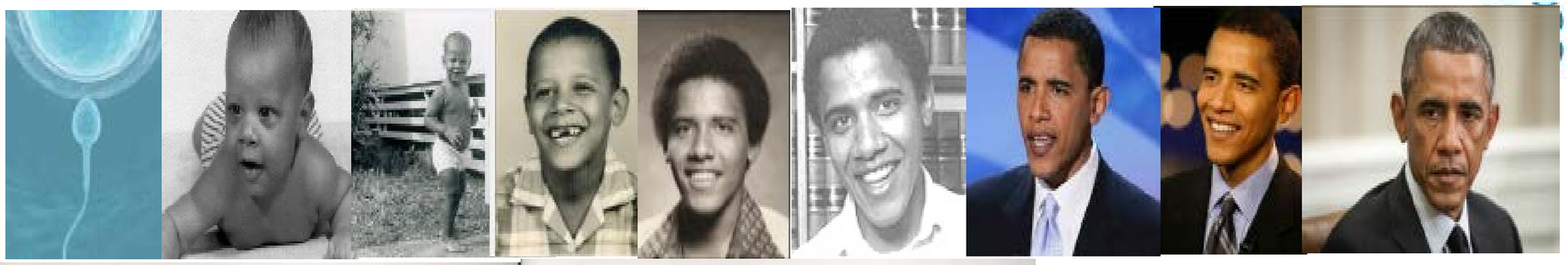


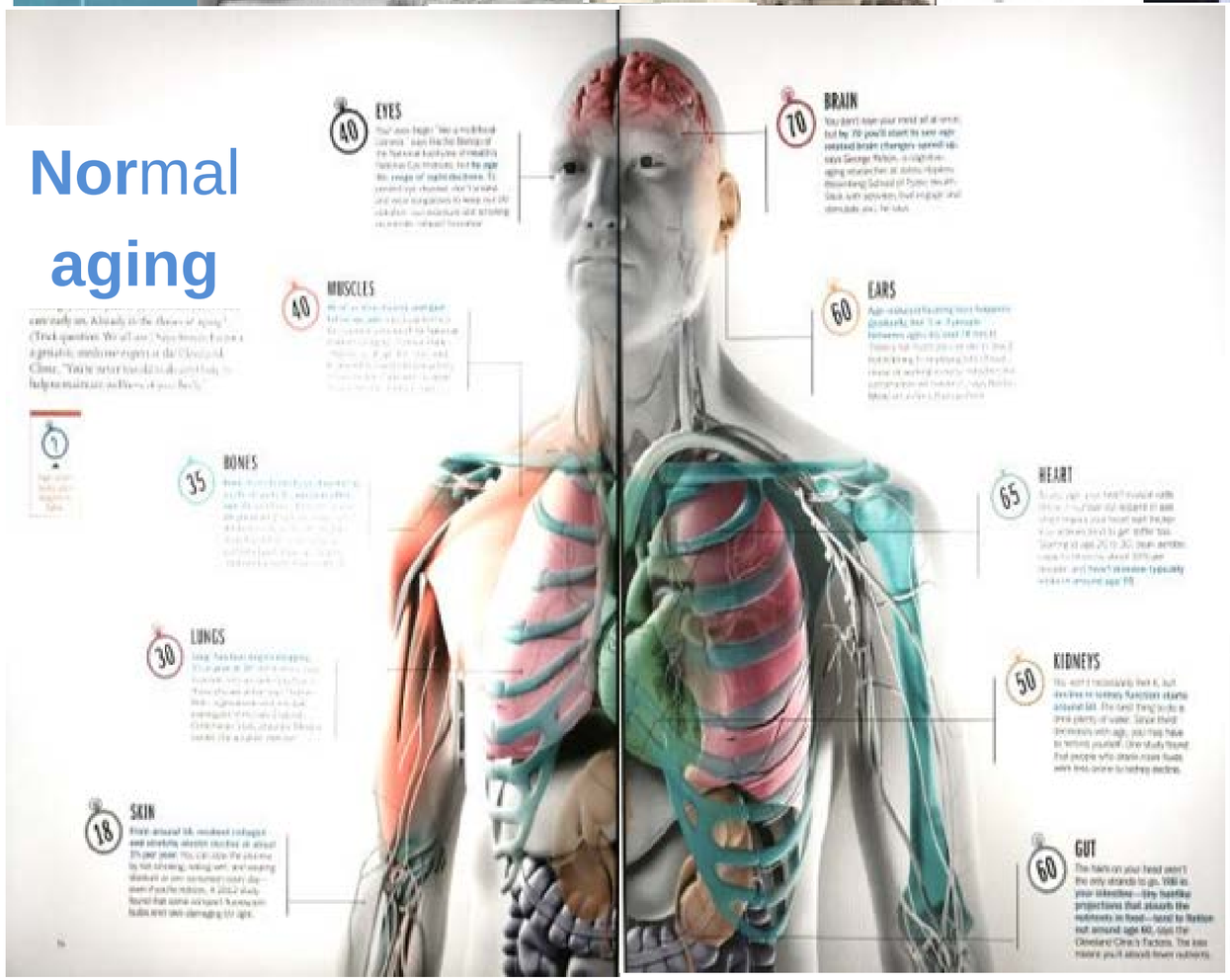
Canadian Perspective

Is Aging
A Chronic Disease ?

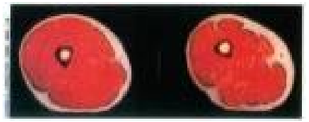


We Become So Much More Vulnerable with Aging





Muscle loss naturally begins around the age of 30 and continues into our 60's at a rate of 1 to 2% of loss each year and accelerates after 60 to as high as 3 to 5% loss annually



The World's Population is Aging: U.S. Health Statistics & Impact

By 2030, the U.S. population aged 50 or over will increase to 132 million. In this time, the number of adults aged 65-74 will nearly double from 21.7 million in 2010 to 38.6 million in 2030.

132 Million — In the next 20 years, the population aged 50+ will increase from 109 to 132 million.

1 in 5 — People will be 65 and over in 2030.

1 in 8 — People will be 75 and over in 2040.

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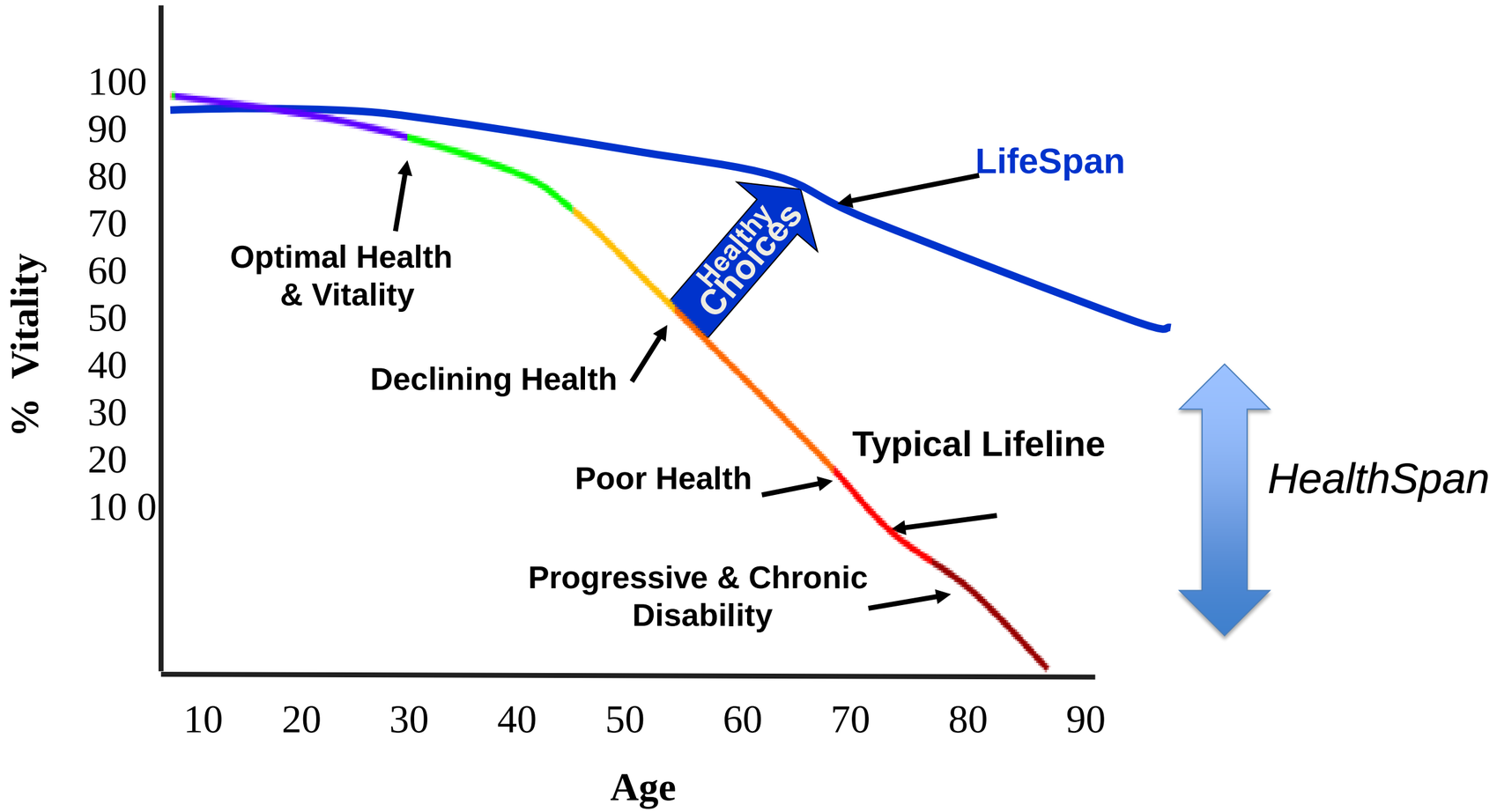
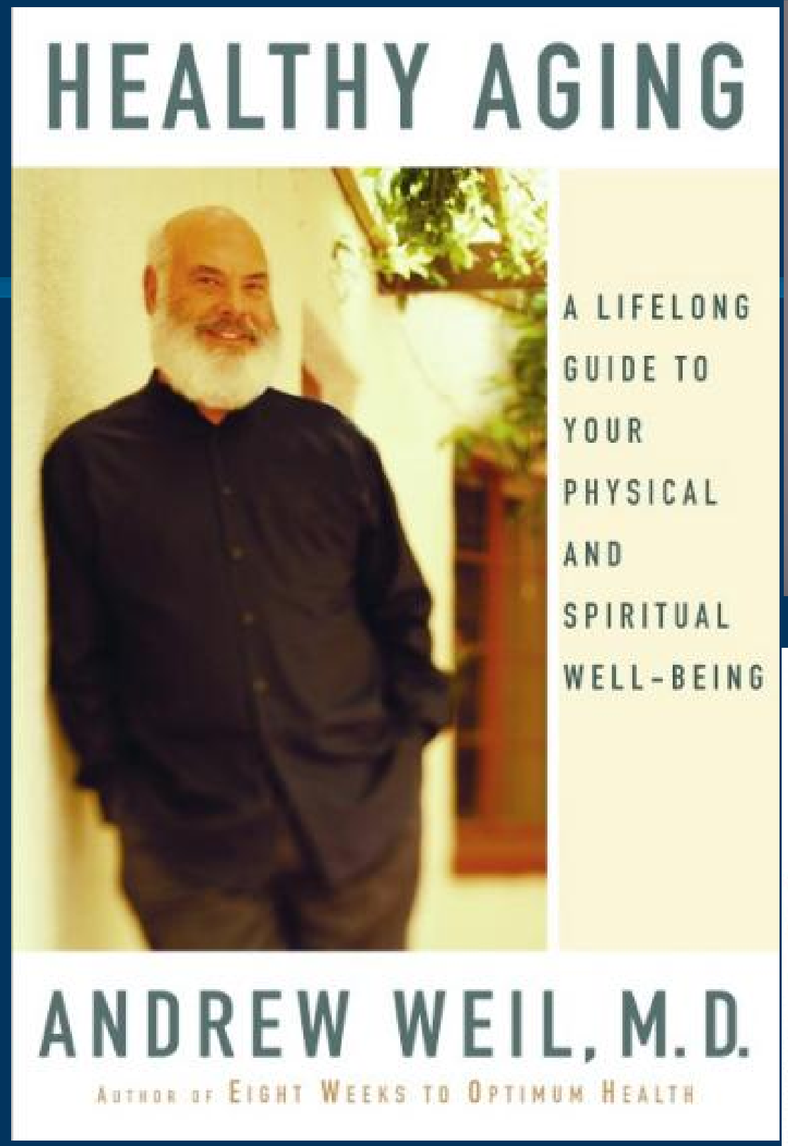
http://www.jchs.harvard.edu/

[(1) Centers for Medicare & Medicaid Services (2) Centers for Disease Control and Prevention (3) United States Bureau of the Census

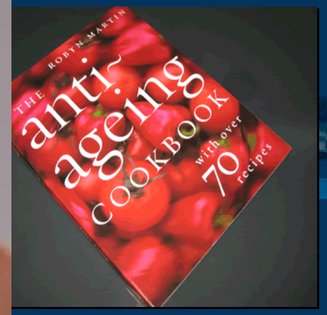
Successful Aging



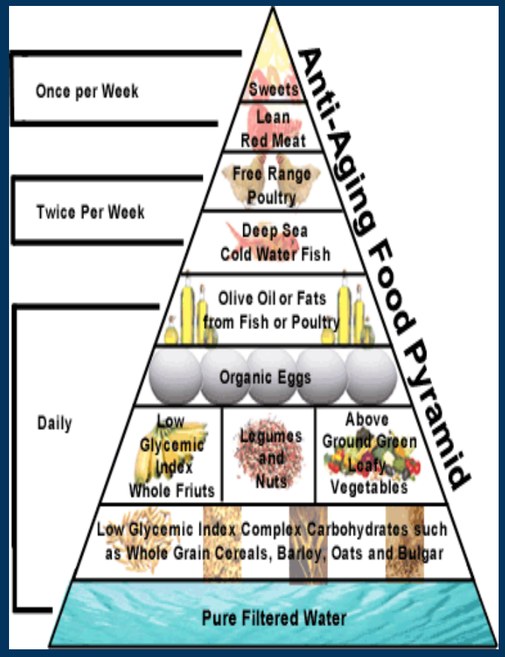
Fries J. *NEJM*. 1980; 303:130-135.
Vita AJ, et al. *NEJM*. 1998;338:1035-1041.


HEALTHY AGING
A LIFELONG GUIDE TO YOUR PHYSICAL AND SPIRITUAL WELL-BEING
ANDREW WEIL, M.D.
AUTHOR OF EIGHT WEEKS TO OPTIMUM HEALTH


50 AND OVER
HEALTHY AGING
EXERCISE, NUTRITION


THE
anti-ageing
COOKBOOK
with over
70
recipes


HEALTHY AGING

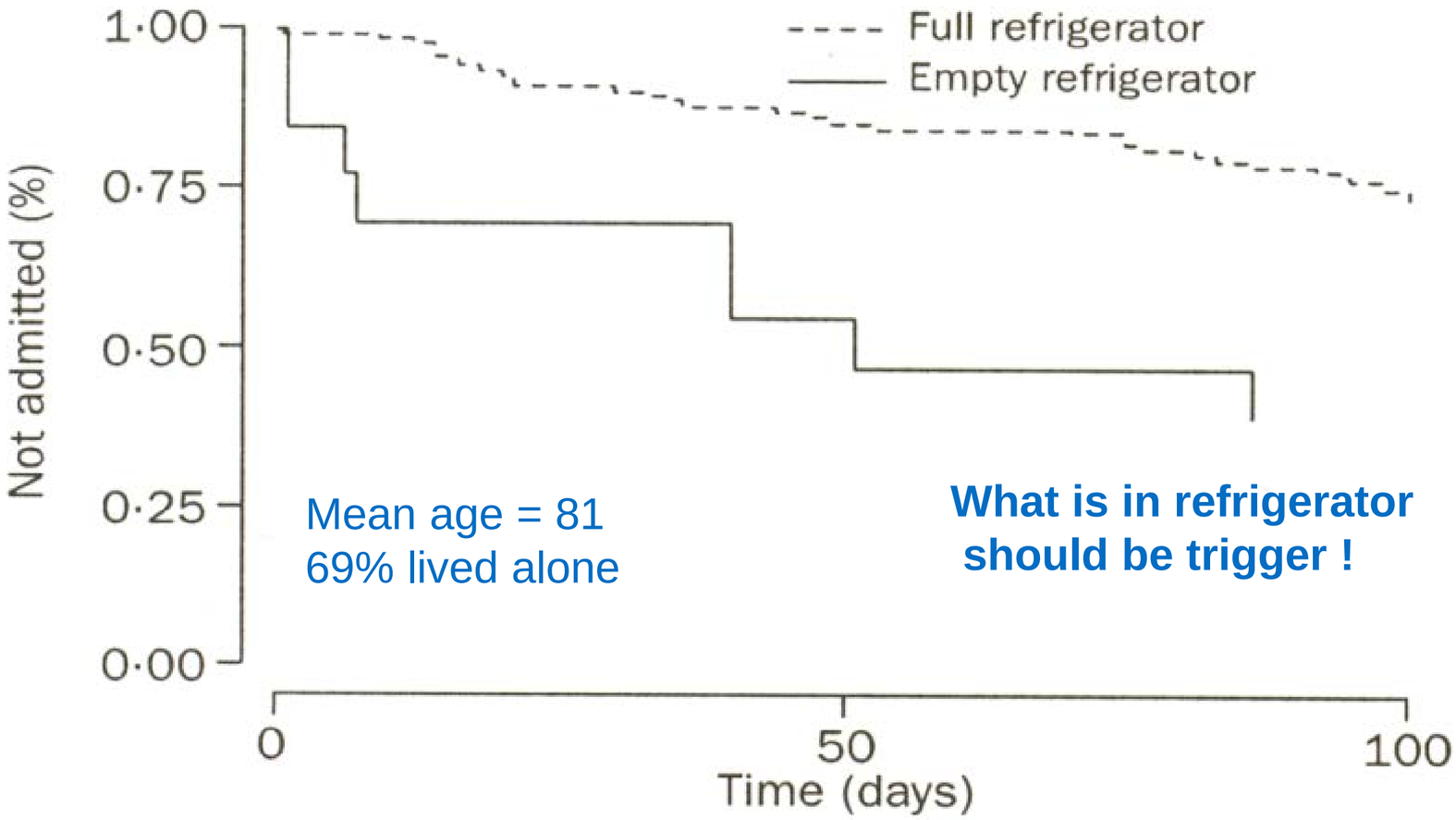

Anti-Aging Food Pyramid
Once per Week
Twice Per Week
Daily
Sweets
Lean Red Meat
Free Range Poultry
Deep Sea Cold Water Fish
Olive Oil or Fats from Fish or Poultry
Organic Eggs
Low Glycemic Index Whole Friuts
Legumes and Nuts
Above Ground Green Leafy Vegetables
Low Glycemic Index Complex Carbohydrates such as Whole Grain Cereals, Barley, Oats and Bulgar
Pure Filtered Water

Prevalence of Malnutrition in the Elderly

Community Dwelling Elderly Populations	% Malnutrition
Mobile Elderly	5-12%
Medical outpatient, Frail elderly	11-20%
Nursing home elderly	23-85 %
Hospitalized elderly	32-50%

Thomas DR, Clin Geriatr Med 2002

What is in Your Refrigerator ?



Mean age = 81
69% lived alone

What is in refrigerator should be trigger !

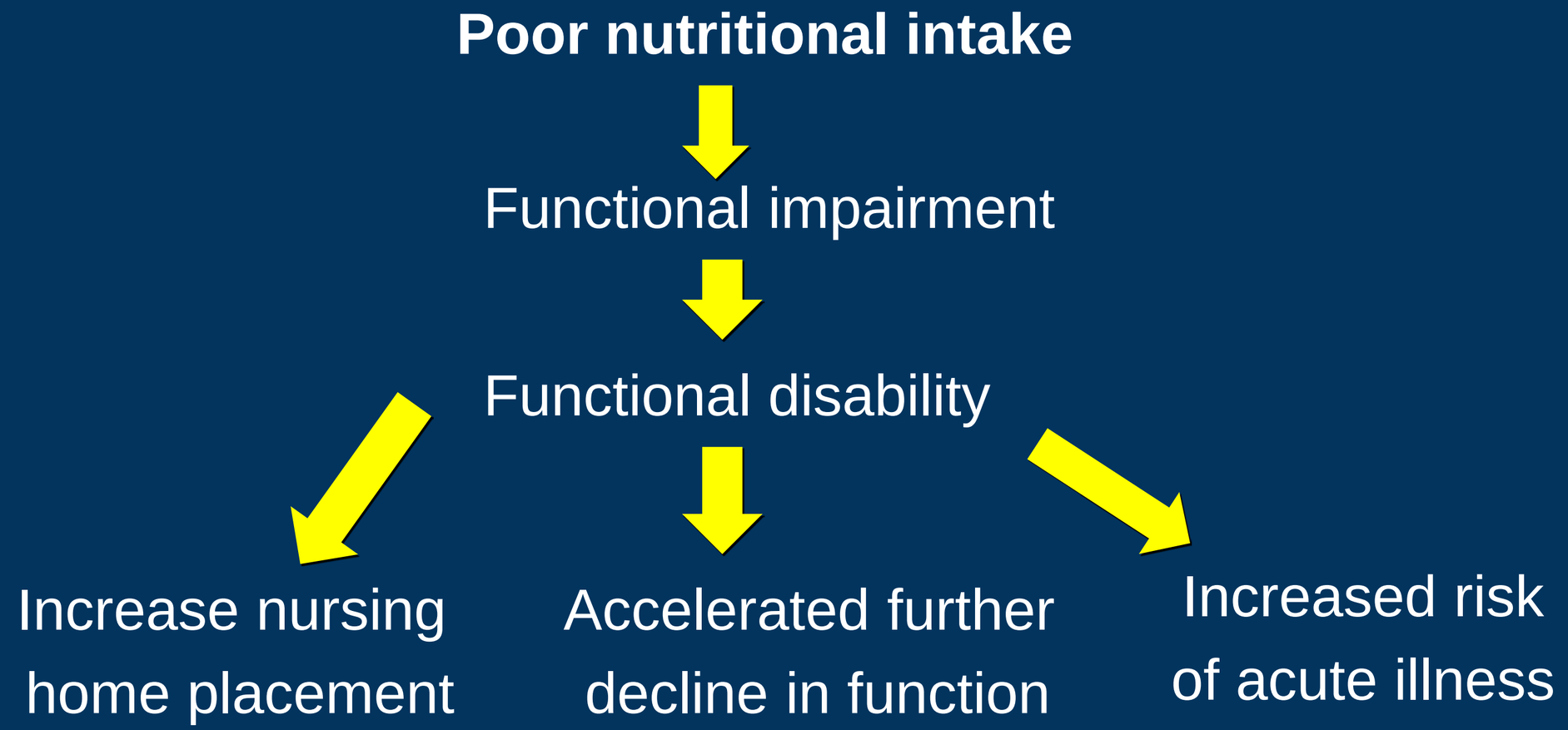
Kaplan-Meyer curves of risk of admission according to refrigerator status

Log-rank test: p=0·006 at 30 days, p=0·812 at 60 days, and p=0·458 at 90 days.

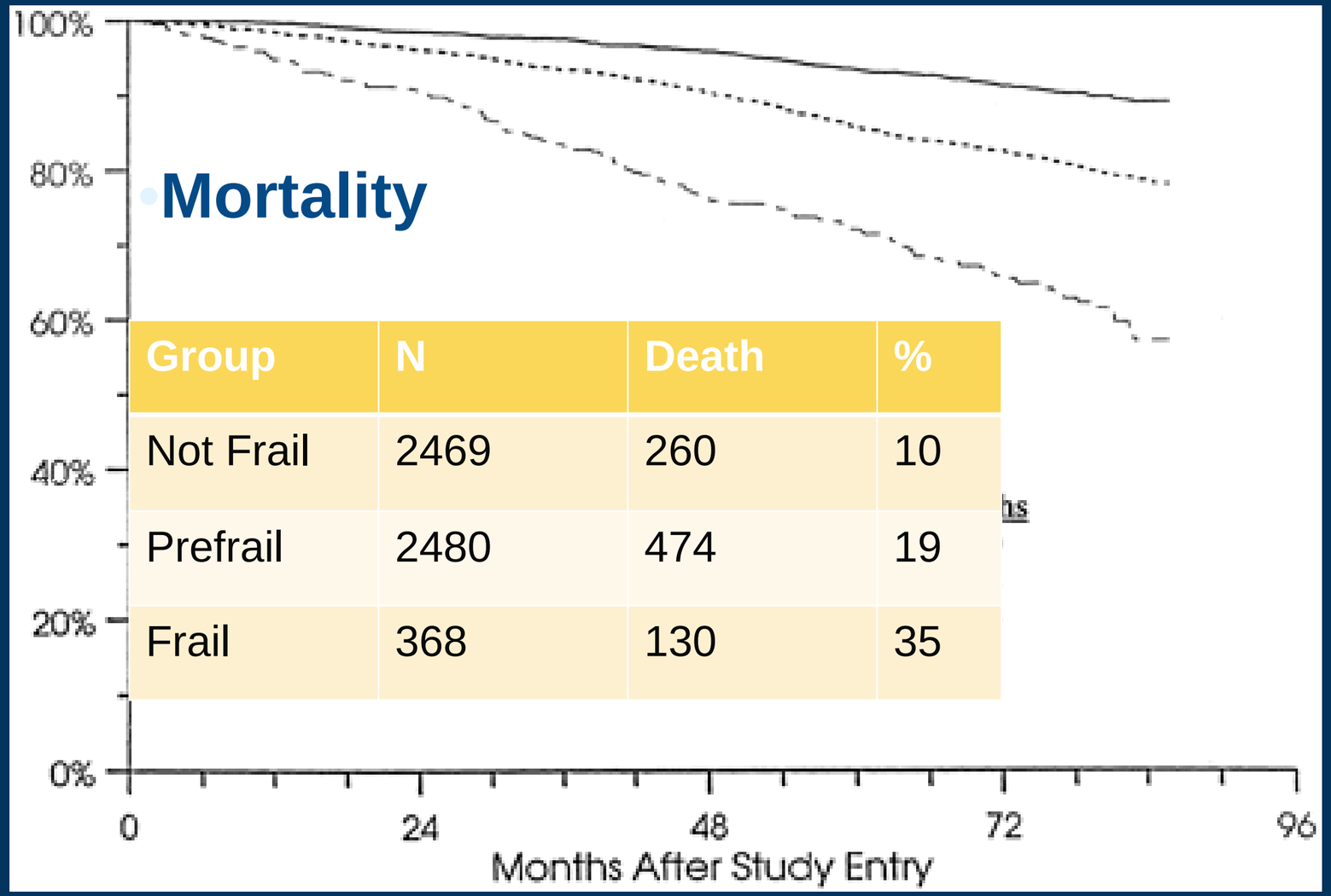
Boumendjel N et al. Lancet 2000;356:563

Frailty

Nutrition Can Influence the “Transition to Frailty and Disability”



Frailty and survival



Group	N	Death	%
Not Frail	2469	260	10
Prefrail	2480	474	19
Frail	368	130	35

Fried Frailty index: wt loss, exhaustion weakness, slowness low physical activity (gait speed, hand grip strength (need 3 of these to meet criteria)

Fried et al., J Gerontol Med Sci 2001;56A:M146-M156

Why are the elderly at higher risk ?

- **Pre-existing malnutrition**
  - **Up to 44 % with some deficiency**
- **Pre-existing sarcopenia**
  - **Frailty associated with ICU mortality**
    - » **84% have died by 6 month**
- **Anabolic resistance**
- **Protein handling**

Kizilarslanglu MC et al Aging Clin Res 2016

Sarcopenia is an Age Associated Health Issue

80% of men and women 35 to 80 years experience moderate to severe muscle loss

40% of consumers 50 & older do not consume the minimally recommended amount of protein

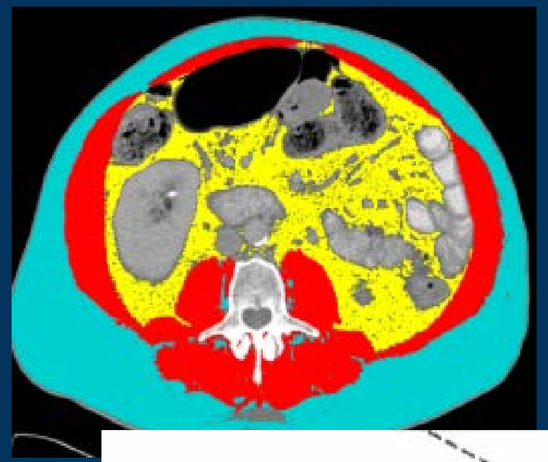
Protein intake after age 40 must include high levels of certain amino acids able to overcome the resistance muscles have as we age.

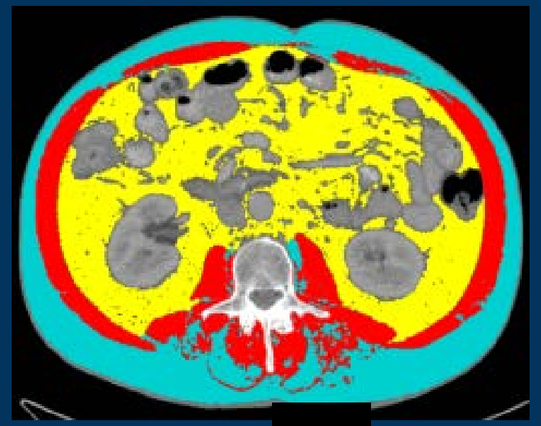
Muscle Loss naturally begins around the age of 30 and continues into our 60's at a rate of 1 to 2% of loss each year and accelerates after 60 to as high as 3 to 5% loss annually.

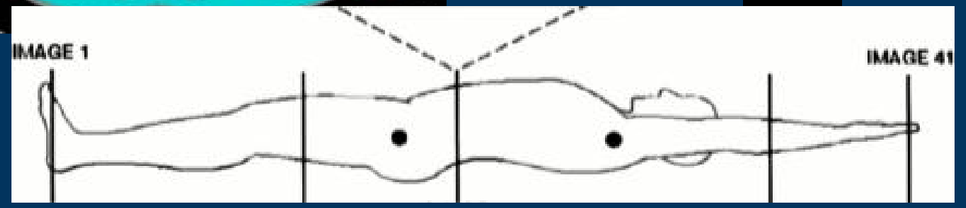
By the time we reach 80, we may have lost up to 50% of muscle vs when we were 30.

Body composition X-sectional imaging

The coming assessment tools !

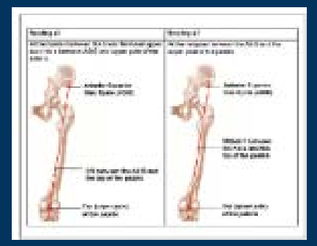




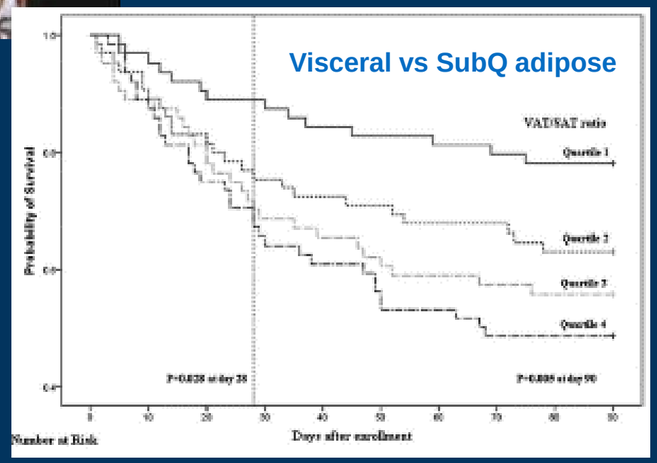


Diseases now proven to have correlated outcome and body composition.

Pancreatic Ca, Colorectal Ca, lymphoma, esophageal Ca, elderly trauma ICU, hepatoma and lung transplant

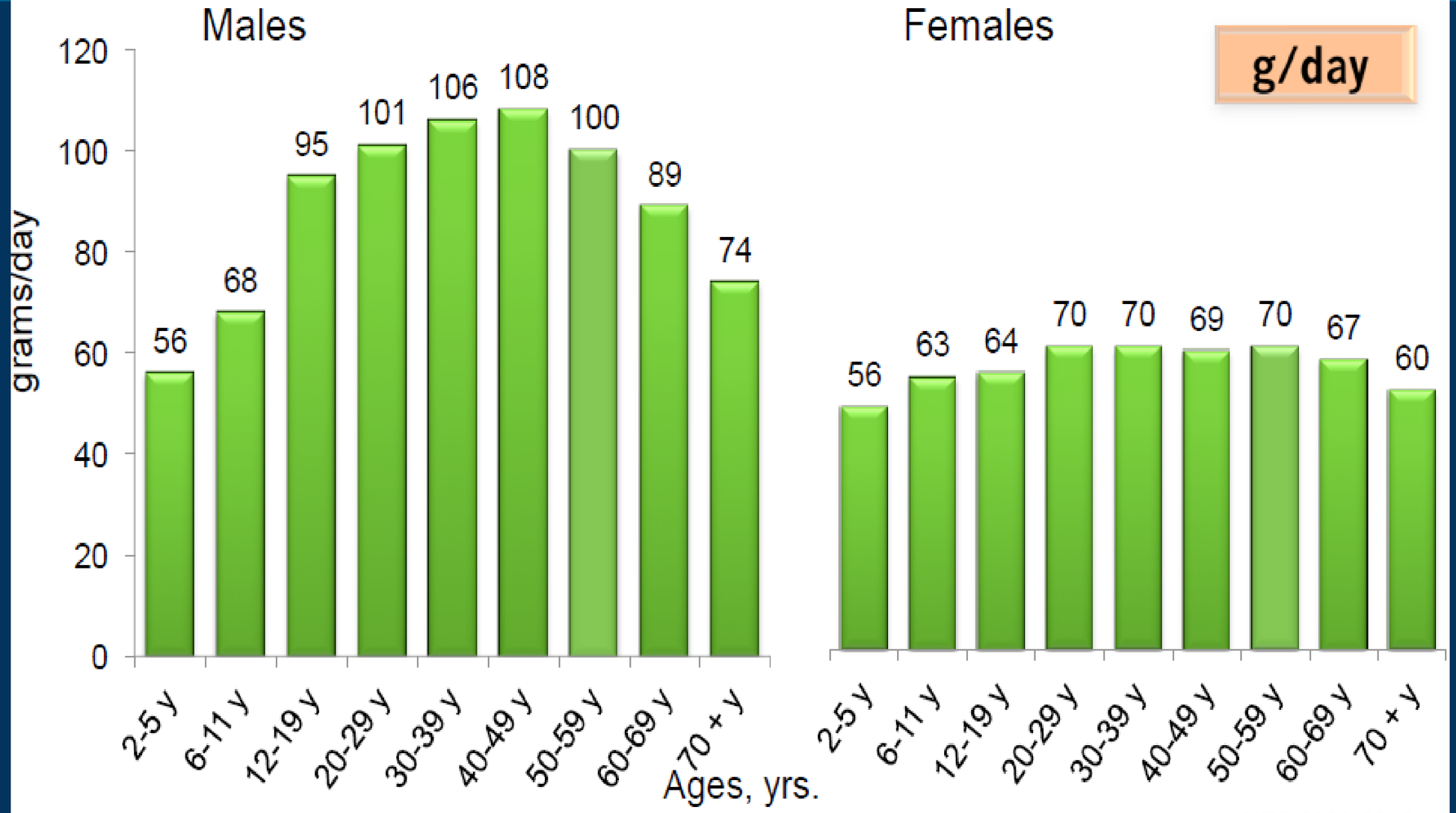


Tillquist M JPEN 2013



1) Peng P J GI Surgery 2012
2) Moisey LL CC 2013
3) Kirk PS et al J Surg Res 2015
4) Okumura S et al Surgery 2015
5) Weig T et al Ann Thor Surg 2016
6) Pisitak C et al CCM 2016

Protein Intake Is Higher in Males and Declines with Age



NHANES 2009-2010

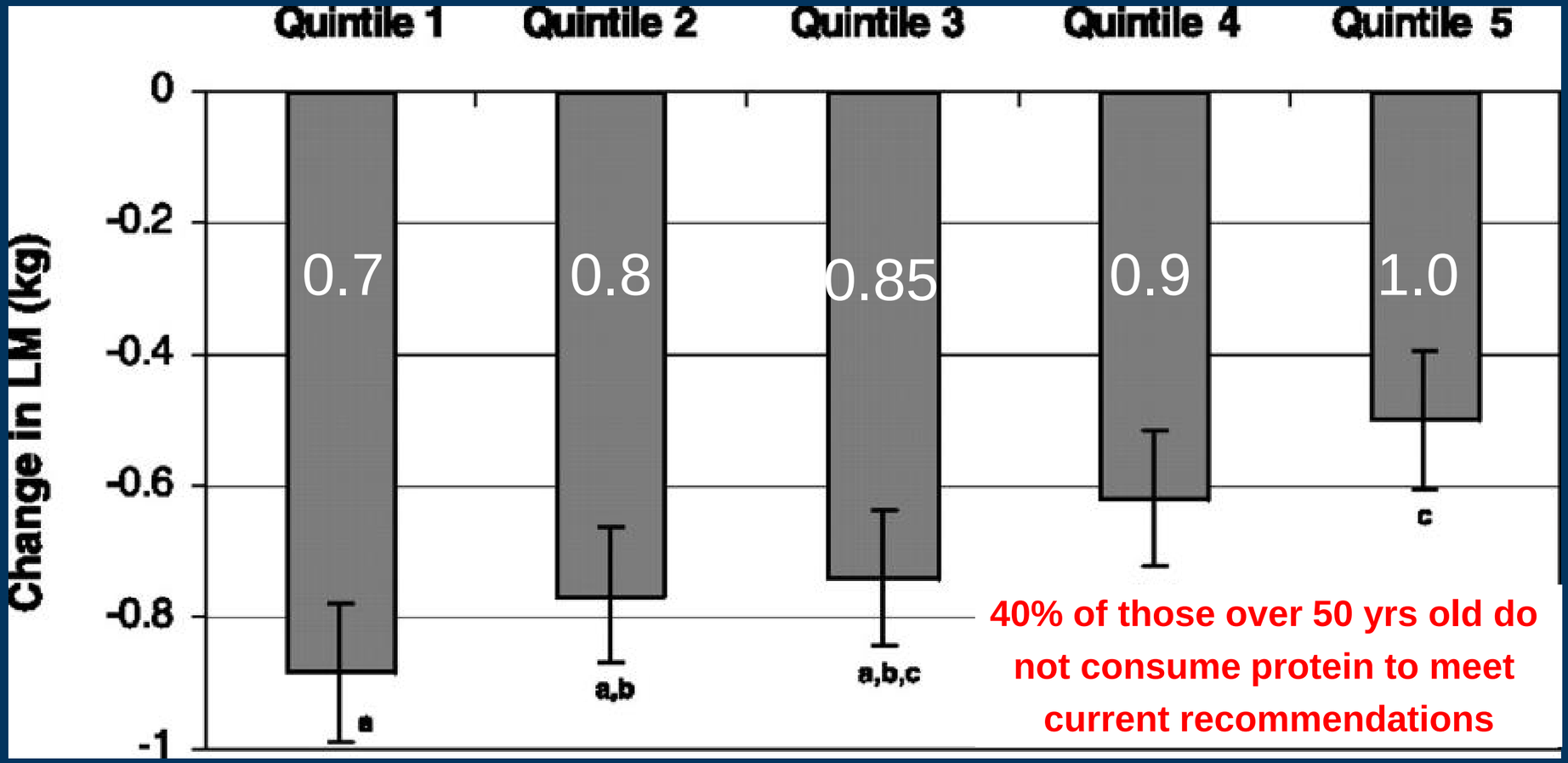
Simple Changes Can Make a Difference !

- **Effects of aquarium in dining-room to caloric intake and weight development**
  - 62 persons in long term care facility
  - Aquarium with living fishes (intervention)
  - Tapestry with sea-side look (control)
  - 16 weeks observational time
  - Significant weight gain in intervention group and diminution of supplement requirements

Edwards NE et al West J Nursing Res 2002;24:697-712

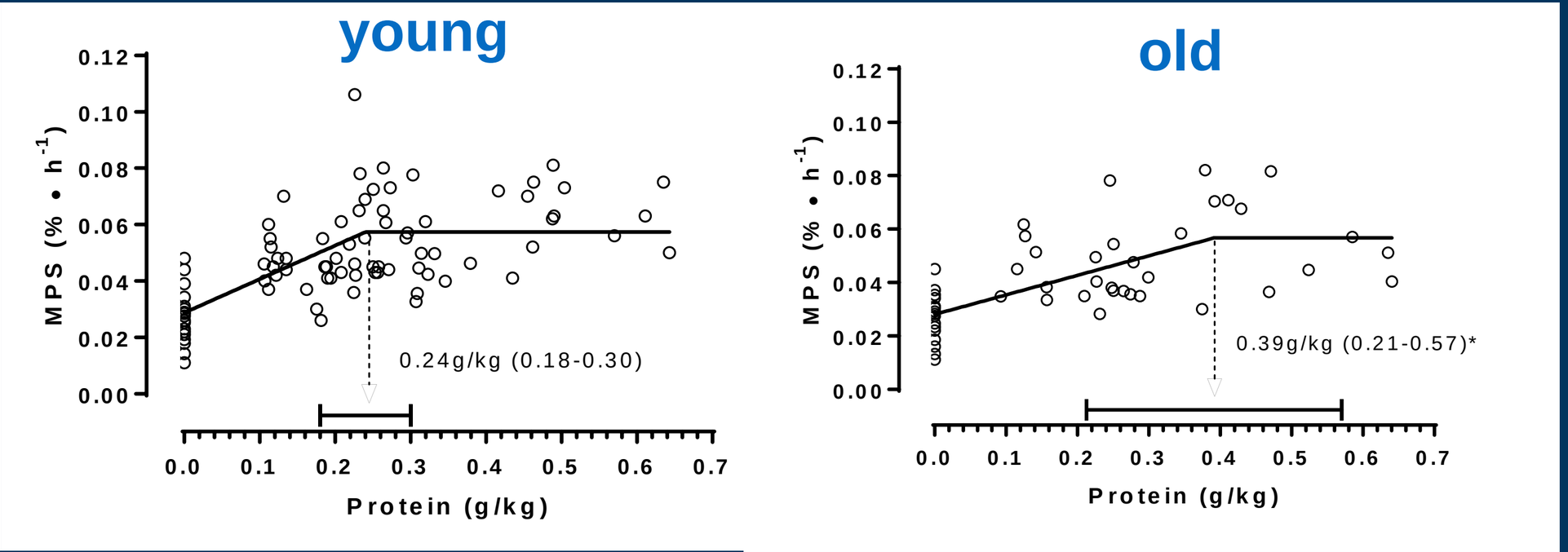
Higher protein intake has been shown to decrease loss of LBM

Adjusted lean mass (LM) loss by quintile of energy-adjusted total protein intake. n = 2066.



Houston D K et al. Am J Clin Nutr 2008;87:150-155

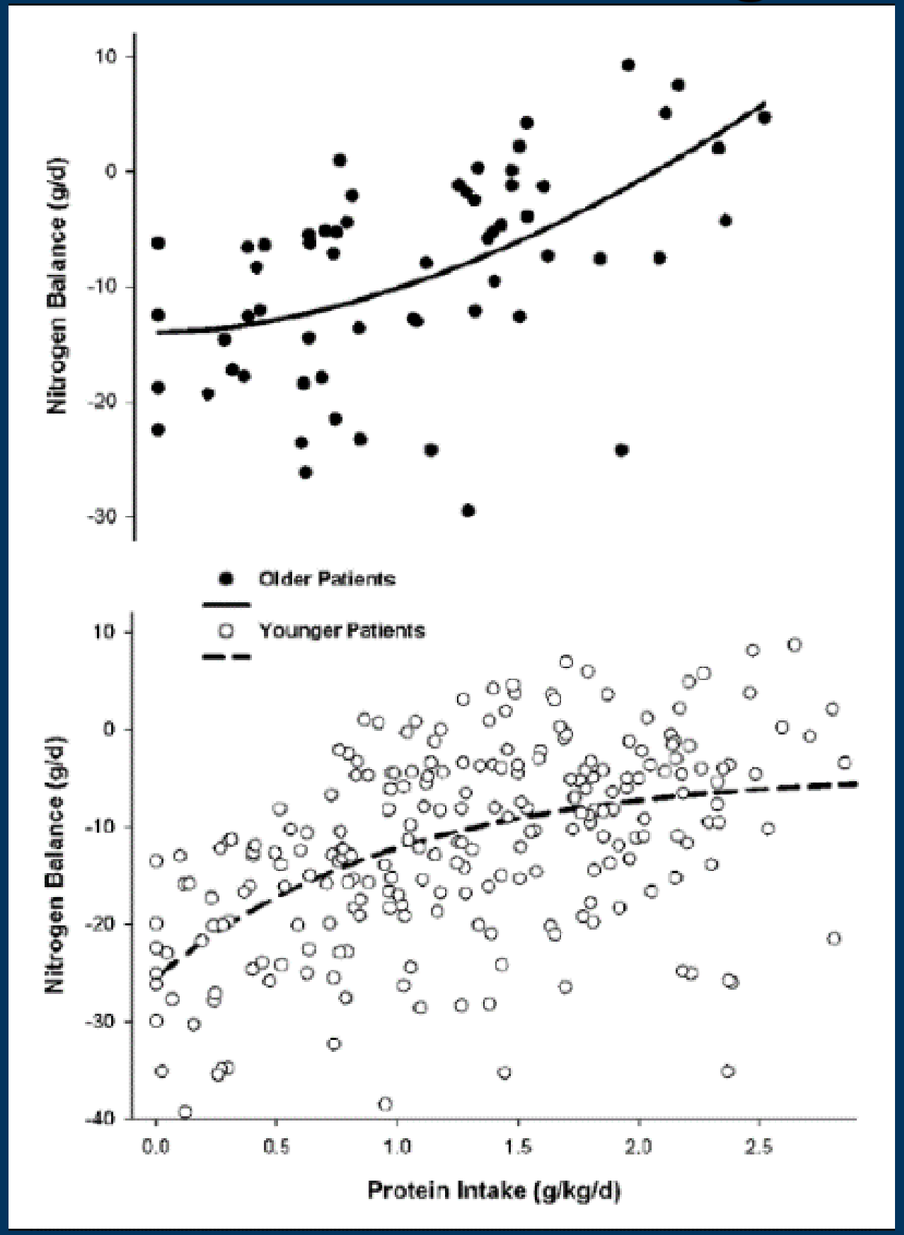
Older men require more protein to optimally stimulate muscle protein synthesis versus young men



MPS = Muscle Protein Synthesis

Moore et al. ***J. Gerontol. A Biol. Sci. Med. Sci.*** **70(1): 57-62, 2015**

Trauma Patients Nitrogen Balance: young vs old



> 65 yo

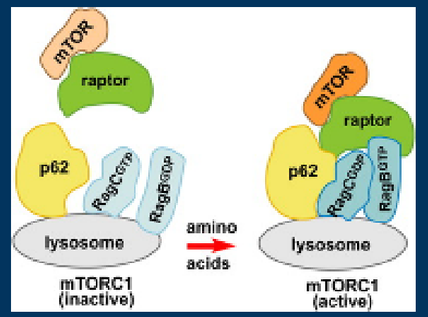
Note: a much higher protein level is required in > 65 yo before curve turns positive direction

< 65yo

Dickerson R et al JPEN 2015

Regulation of mTORC1 by amino acids

Liron Bar-Peled[1] and David M. Sabatini[2,3,4,5]



- mTOR pathway
  - Master regulator of cellular, organ and organismal growth
    - » Nutrient sensing coupled to long range growth and hormonal signaling networks
    - » Conserved evolutionarily from yeast to mammals
- mTOR
  - Atypical serine-threonine kinase key component in two distinct multi-protein complexes mTORC1 and mTORC2
    - » mTOR1- cell growth (generally)
      - » Relies on downstream effectors to coordinate anabolic programs (ex. mRNA translation)
      - » Represses catabolic programs such as autophagy
    - » mTOR2 - promotes cell proliferation and survival

Bar-Peled L et al Trends in Cell Biology 2014

  - AA levels are critical to mTORC1 activation
  - Leucine and arginine are required for mTORC1 activation but are insufficient for its activation in cells deprived of remaining 18 AA

Is anabolic resistance of elderly real ?

- Failure of normal anabolic stimuli to induce mRNA translation – effector via the mTORC

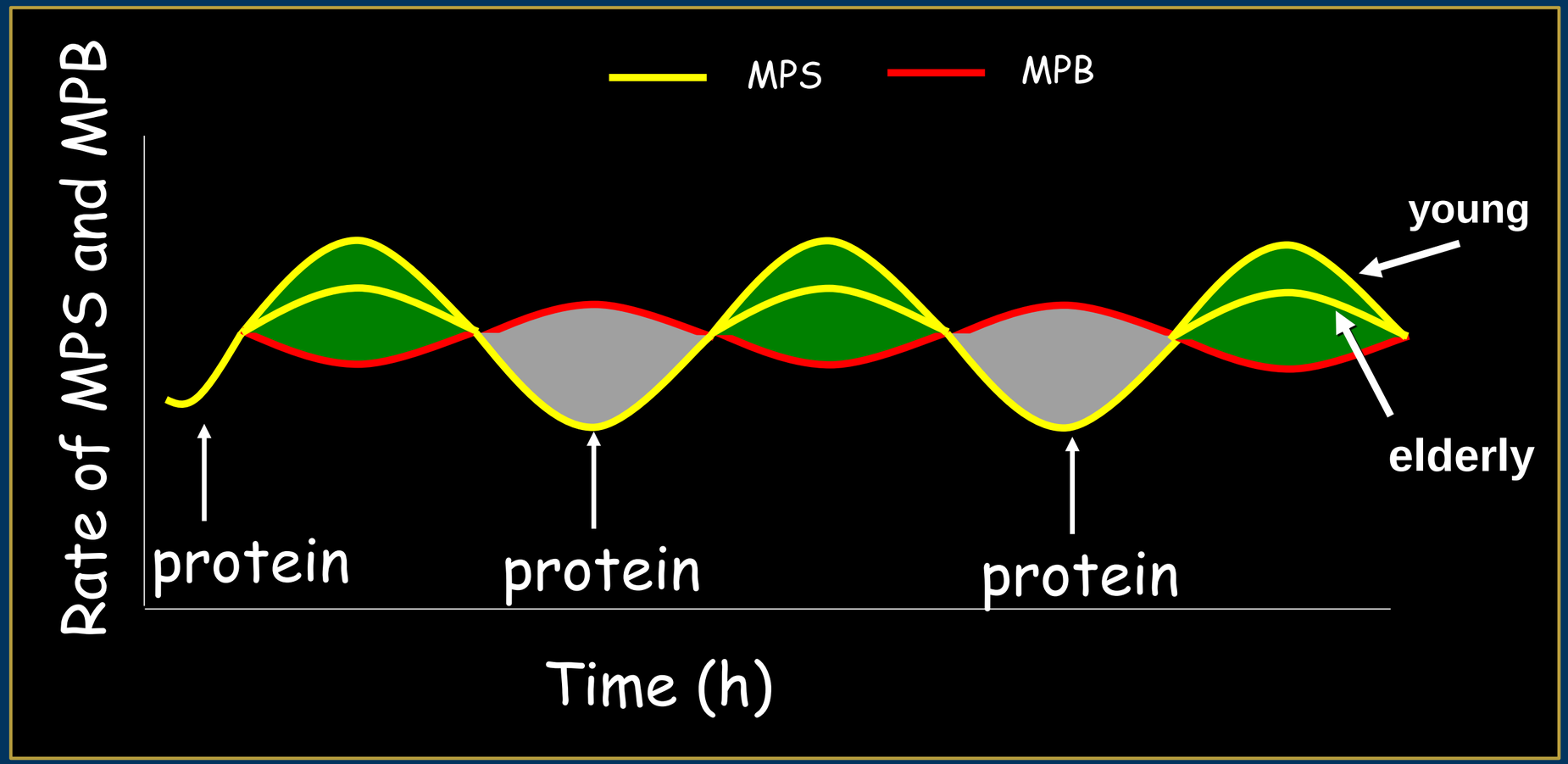
- Factors partially explaining anabolic resistance
  - Leucine insensitivity
    - Blunted response to anabolic AA stimulus
  - Splanchnic sequestration following normal feeding
  - Decreased AA availability and uptake in muscle

  - Insulin induced microvascular perfusion blunted
  - Attenuated insulin induced suppression of muscle catabolism

Moore DR et al Adv Nutr 2014

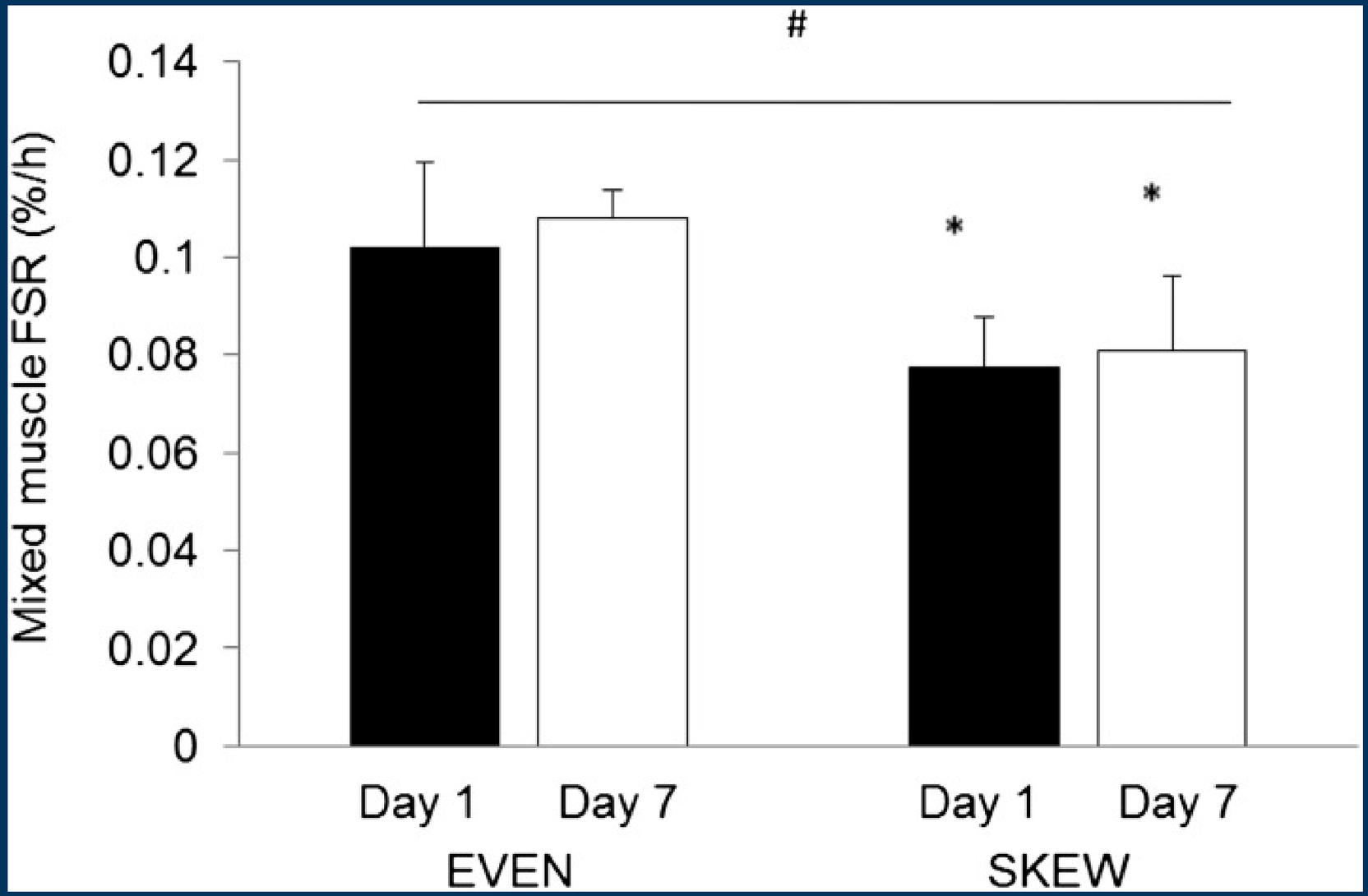
Burd NA, Wolfe R et al J App Physio 2011

‘Anabolic resistance’ of muscle protein in aging



Slide courtesy of Stuart M Phillips

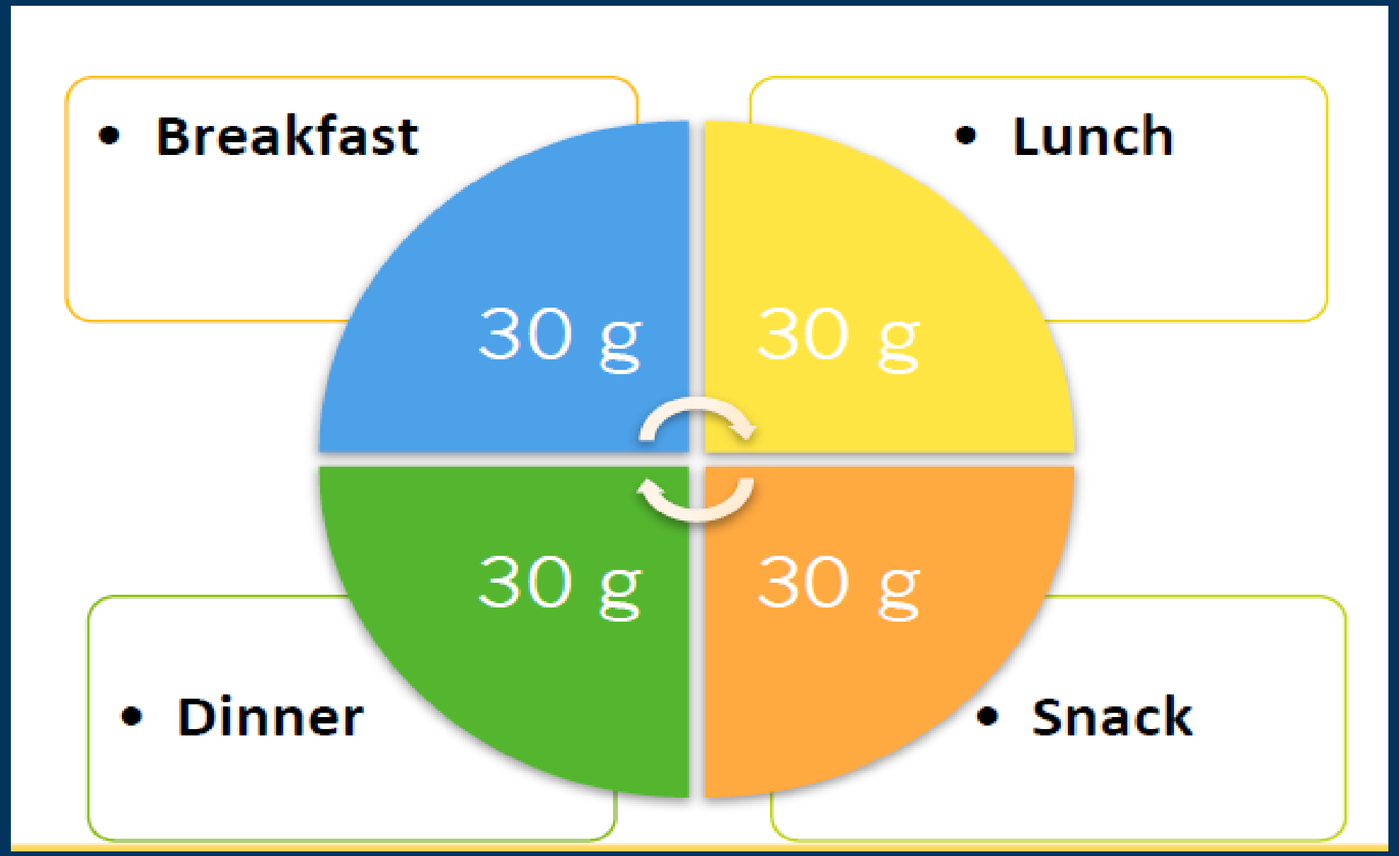
Distribution of protein over a 24h period, does it matter ?



Layman DK et al Am J Nutr 2014

Overcoming the anabolic resistance of aging

Distribute throughout the day: 30-30-30-30 Program



Deutz N Clin Nutrition 2013

Risk Factors: Dementia

Age

Cardiovascular

Lipid metabolism

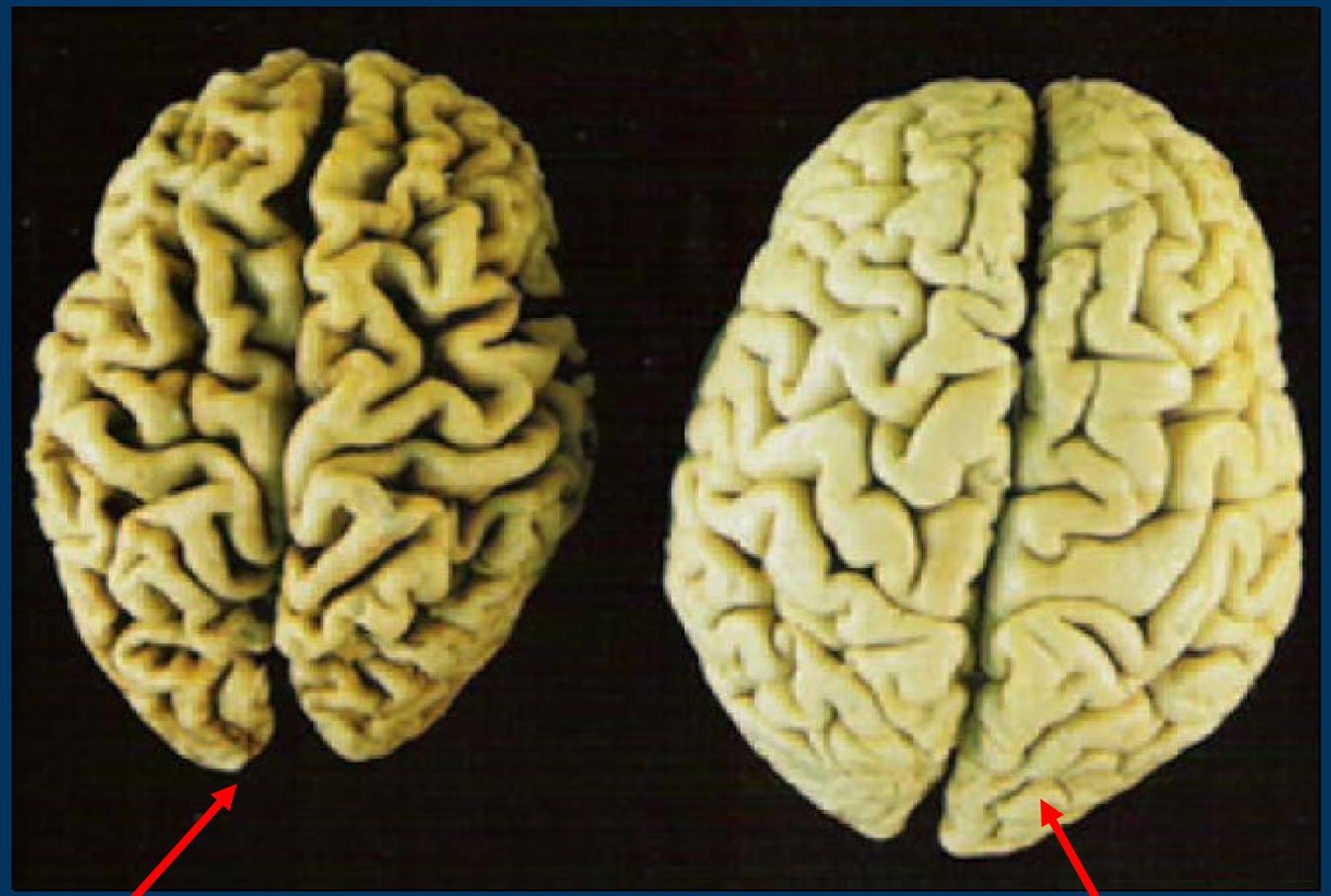
Inflammation

Genetics

Homocysteine ↑

Oxidative stress

Morphology of Dementia?



«Sick Brain

Healthy Brain

Omega 3 fatty acids to decrease cognitive with aging

- Prospective study plasma fatty acids and cognition
- N=2251 patients
- Multiple neuropsychological testing modules
- Hypothesis: oxidative stress related to neurodegenerative disease
- Conclusions:
  - Omega-3 FA have substantial benefit in reducing cognitive decline

Beydoun MA et al .
Am J Clin Nutr 2007; 85:1103-11

- Prospective RCT EPA/DHA supplements in cognitive function
- N= 867 > 70 yo
- 200 mg EPA/500 mg DHA vs olive oil for 24 months.
- Conclusion:
  - No difference between groups in loss of cognitive function

Dangour AD et al Am J Clin Nutr 2010,91:1725

“Plasma FO and atrophy of medial temporal lobe”

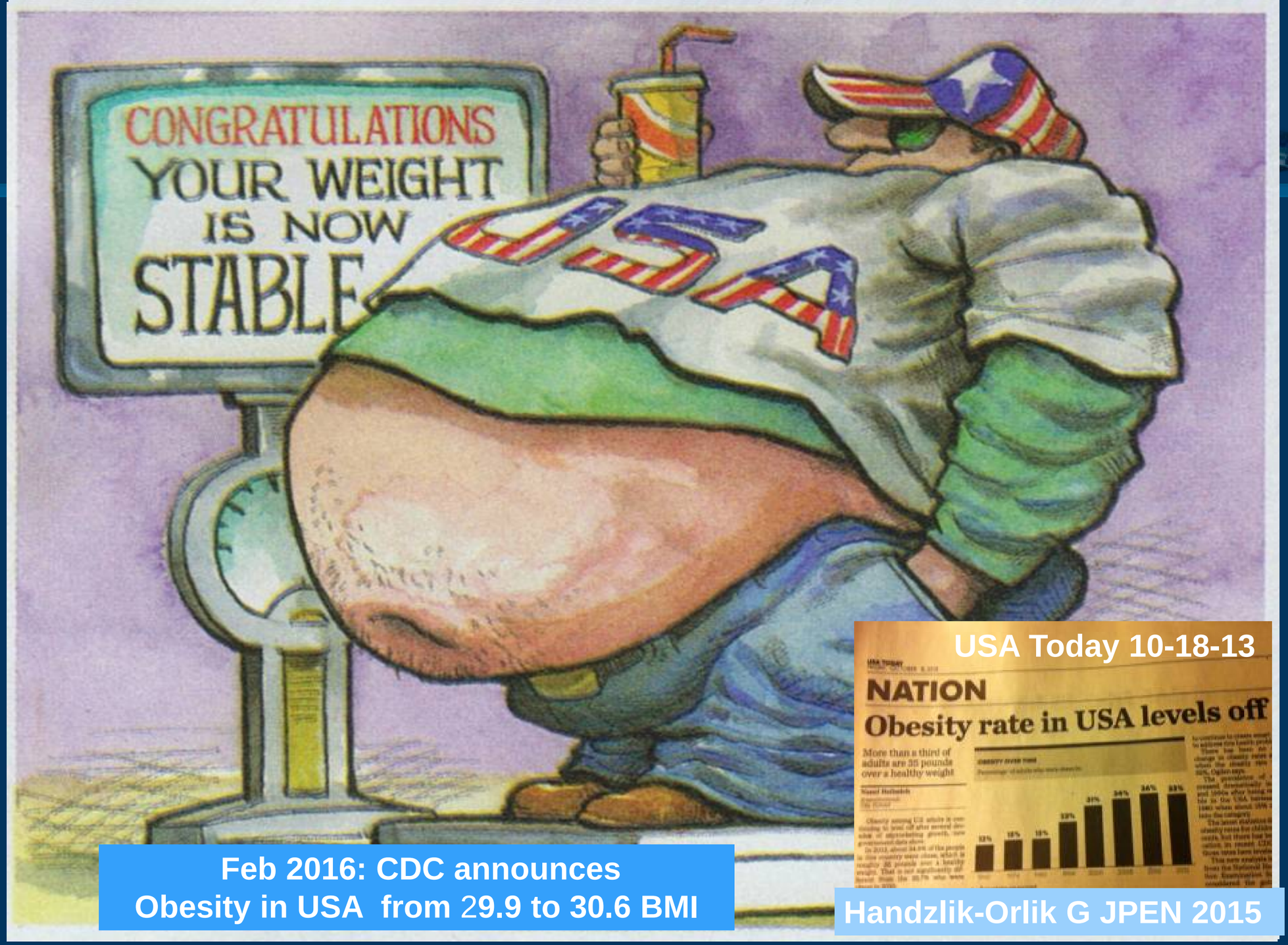
- Prospective observational study
- N=281 (MRI evaluation)
- Objective: associate FO with depression, dementia, Alzheimer Disease
- Results:
  - Higher plasma EPA/DHA less gray matter loss
  - Atrophy associated with lower decline in memory and depression

Samieri C et al Neurology 2012

Specific nutrients or agents with reported benefit in elderly

- HMB (β-hydroxy-β-methylbutyrate)
- Leucine
- AA combinations
  - Gln – arginine
  - HMB-Arginine-Lysine
- Vit D
- Anti-oxidants
- Fish Oils
- Etc etc etc

Deutz NE, et al Clin Nutr 2013 ---HMB
Baier S et al. JPEN 2009 --- HMB-arg-lys



USA Today 10-18-13

NATION

Obesity rate in USA levels off

More than a third of adults are 35 pounds over a healthy weight

Feb 2016: CDC announces
Obesity in USA from 29.9 to 30.6 BMI

Handzlik-Orlik G JPEN 2015

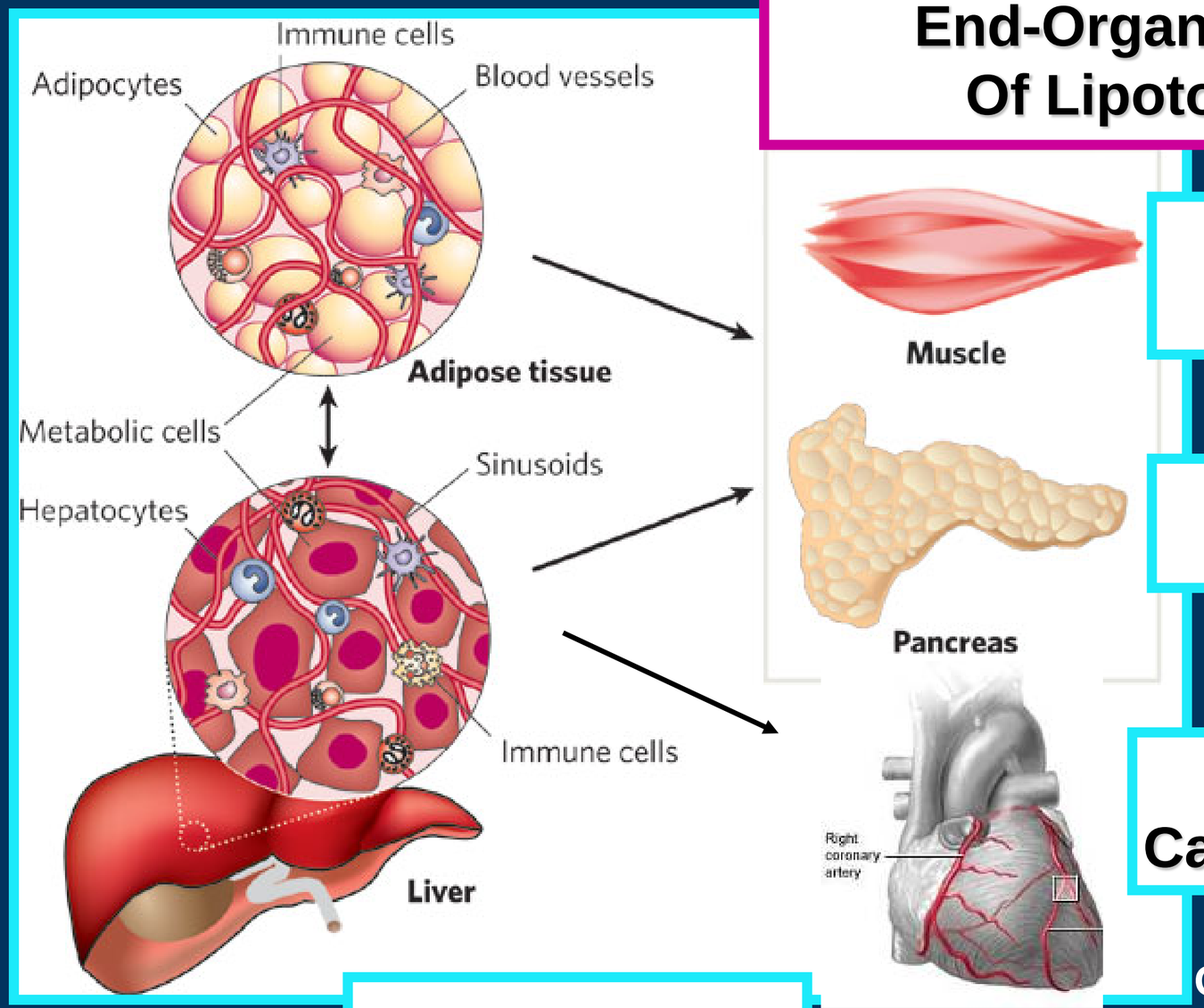
Perception of obesity has dramatically changed

Fat and Jolly

Obesity is disease of inflammation

Guilia M et al J Cell Physiology 2017

End-Organ Effects Of Lipotoxicity



Insulin Resistance

Diabetes

Diabetic Cardiomyopathy

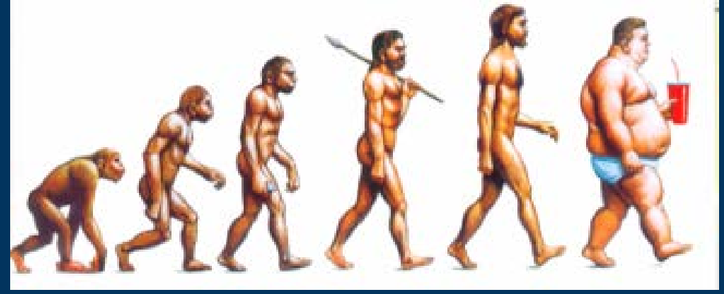
Occurs at a lower BMI in Asian population

NAFLD/NASH

NAFLD= non-alcoholic fatty liver disease
NASH = non-alcoholic steatohepatitis

Gualia M J Cell Physiol 2017

Complications of Obesity



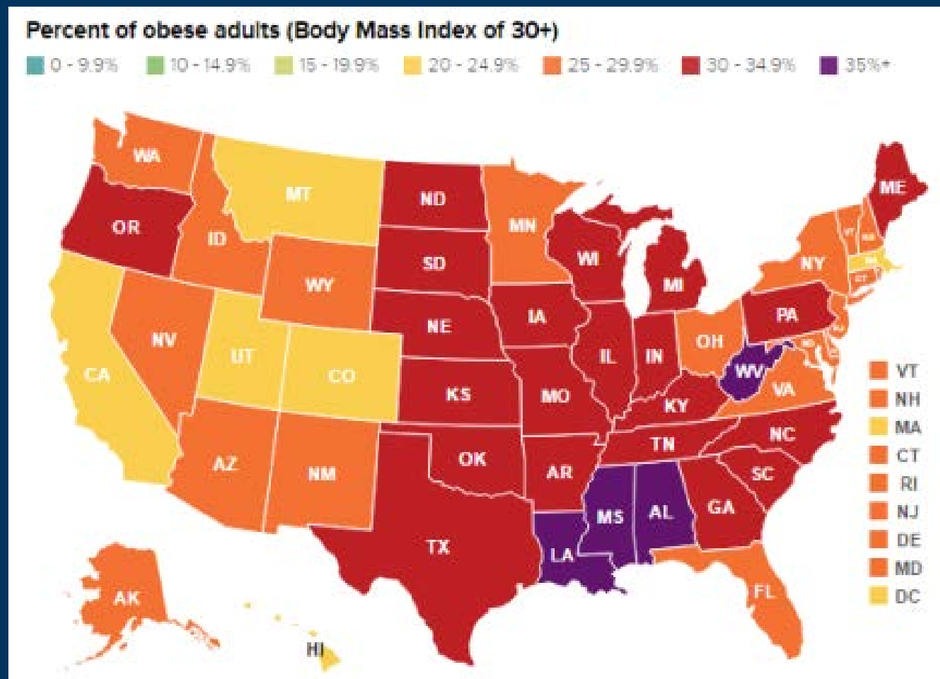
Metabolic	•Diabetes, NAFL, gallstones
Structural	•GERD, pseudotumor cerebri
Inflammatory	•Arthritis, autoimmune disease
Degenerative	•Degenerative joint disease
Neoplastic	•Prostate, breast, ovarian, endometrial, cervical, lymphoma, renal cell
Psychological	•Depression, anxiety panic attacks, eating disorders

60

Proportion of Disease Prevalence Attributable to Obesity

Type 2 diabetes	**57%**
Cancer (fuel that feeds the flame of inflammation)	**33%**
Breast 11%	
Uterine 11%	
Colon 11%	
Gallbladder disease	**30%**
Hypertension	**17%**
Coronary heart disease	**17%**
Osteoarthritis	**14%**

Arnold M et al Cancer Epidemiology 2016
Fong-Burgada, N et al Cell Metab 2015
Wolfe B et al Obes Res 1998
Wolfe B et al LABS Project 2016


Percent of obese adults (Body Mass Index of 30+)
0 - 9.9%
10 - 14.9%
15 - 19.9%
20 - 24.9%
25 - 29.9%
30 - 34.9%
35%+
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
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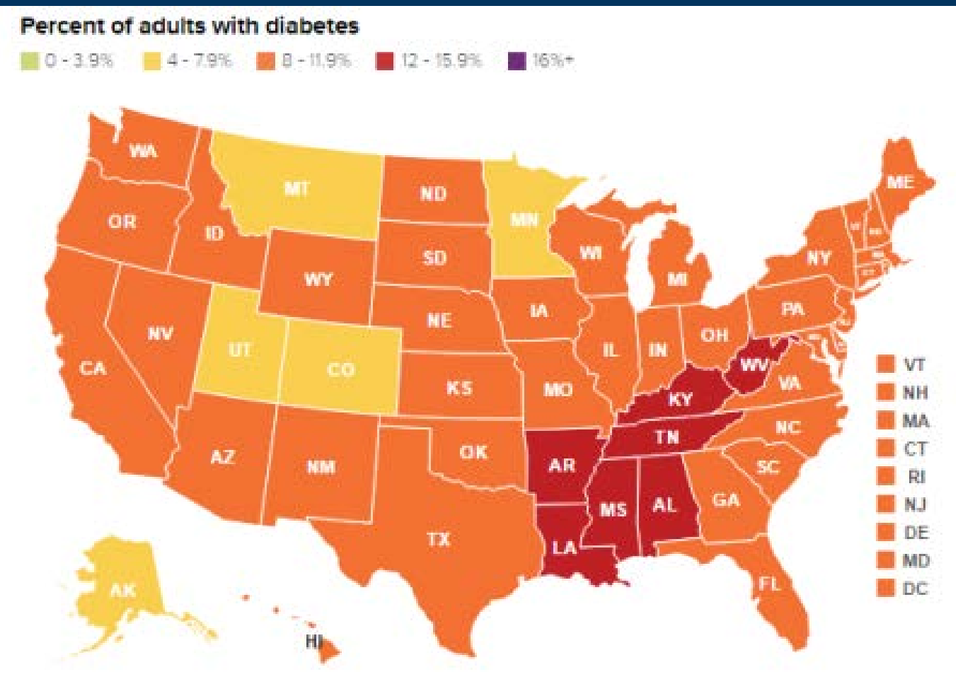
Percent of adults with diabetes
0 - 3.9%
4 - 7.9%
8 - 11.9%
12 - 15.9%
16%+
WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
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ME
AK
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NH
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CT
RI
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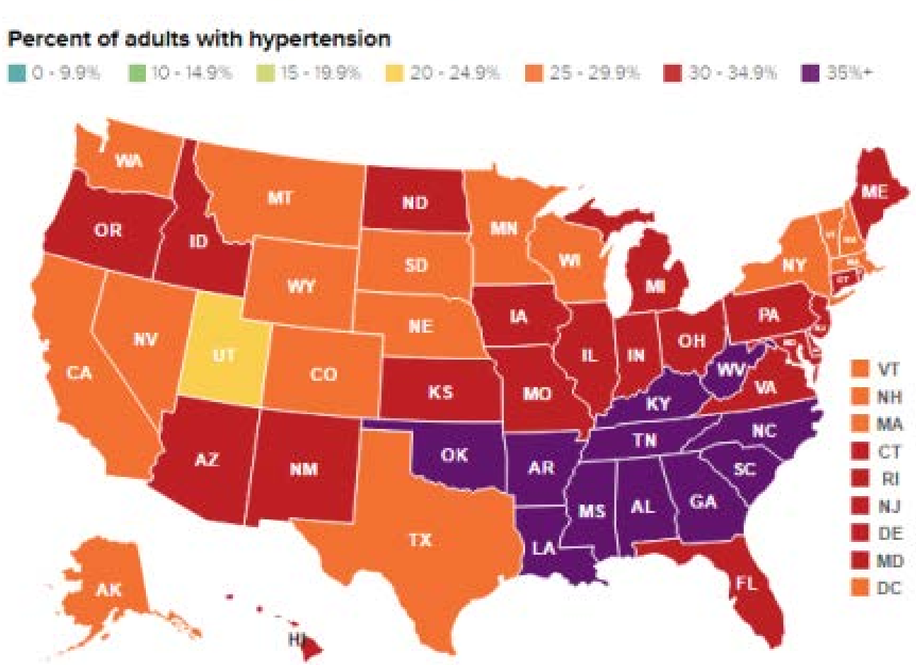
Percent of adults with hypertension
0 - 9.9%
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25 - 29.9%
30 - 34.9%
35%+
WA
OR
CA
ID
NV
MT
WY
UT
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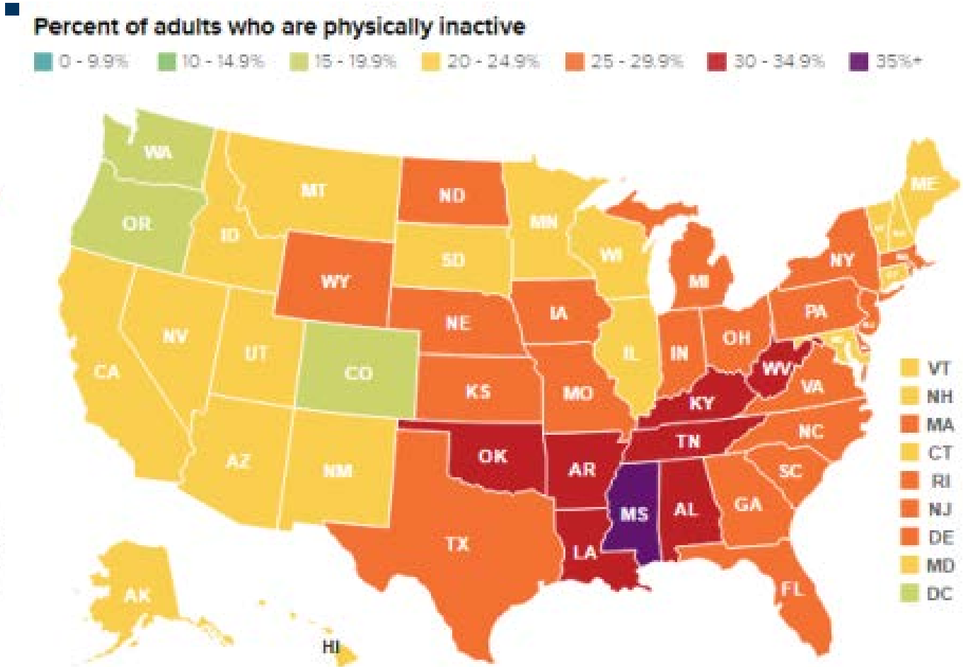
Percent of adults who are physically inactive
0 - 9.9%
10 - 14.9%
15 - 19.9%
20 - 24.9%
25 - 29.9%
30 - 34.9%
35%+
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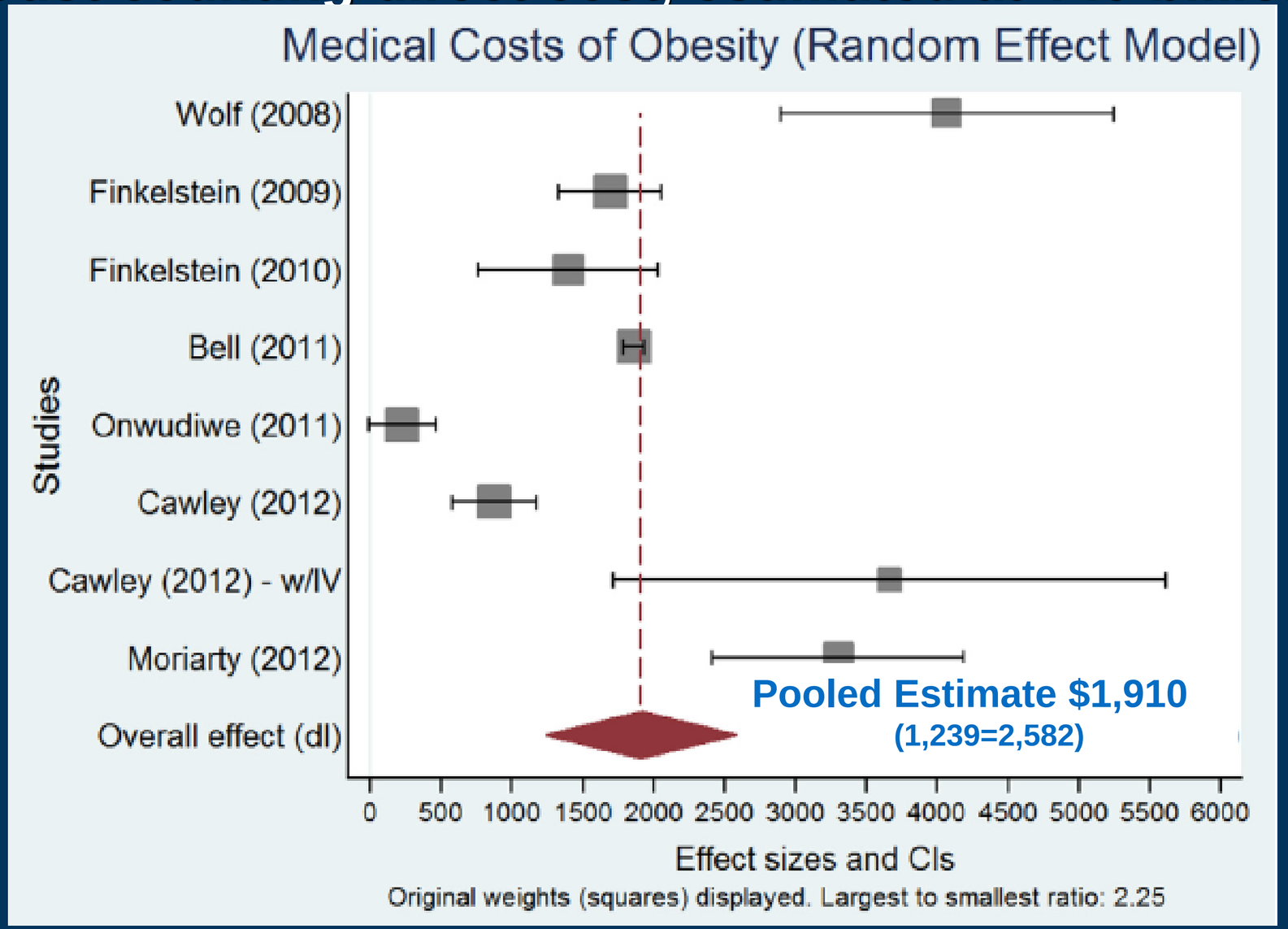
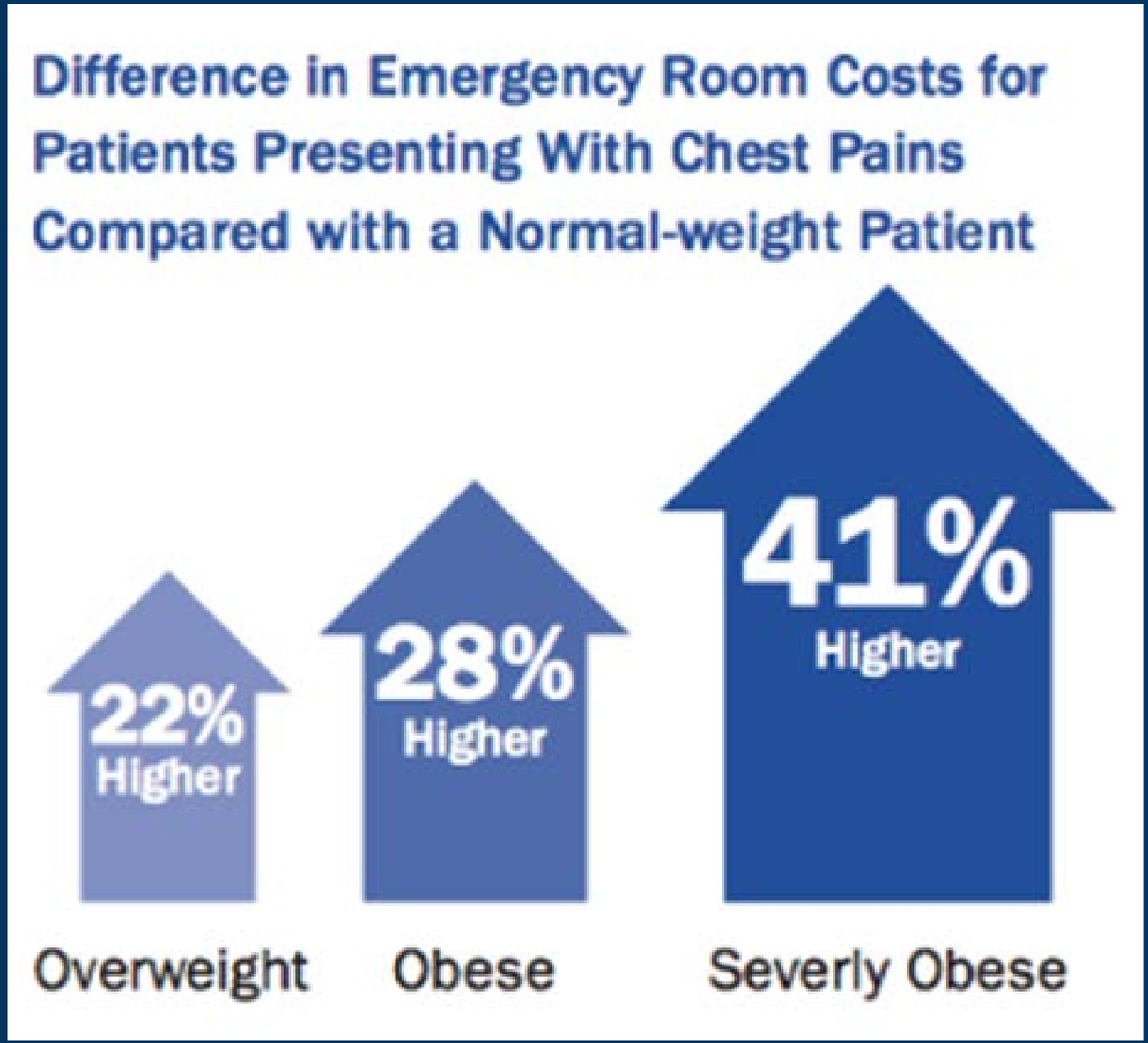
Medical Costs of Obesity

Just counting direct cost, estimated at 149 billion

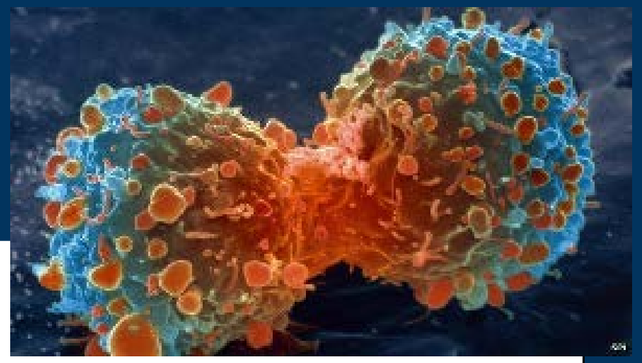


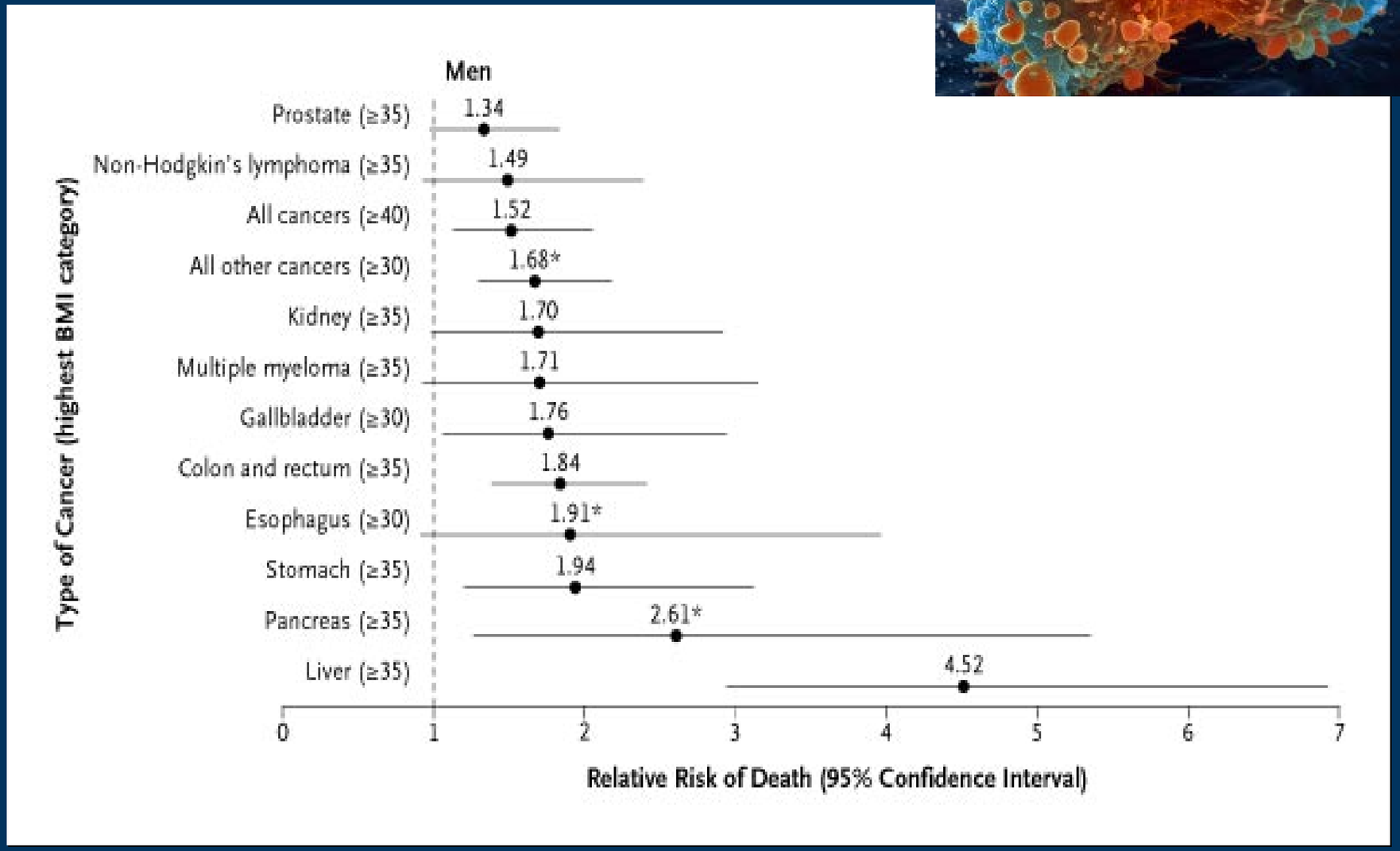
Kim DD et al Value in Medicine 2016

Economic Cost of Obesity on Chest Pain Presentation



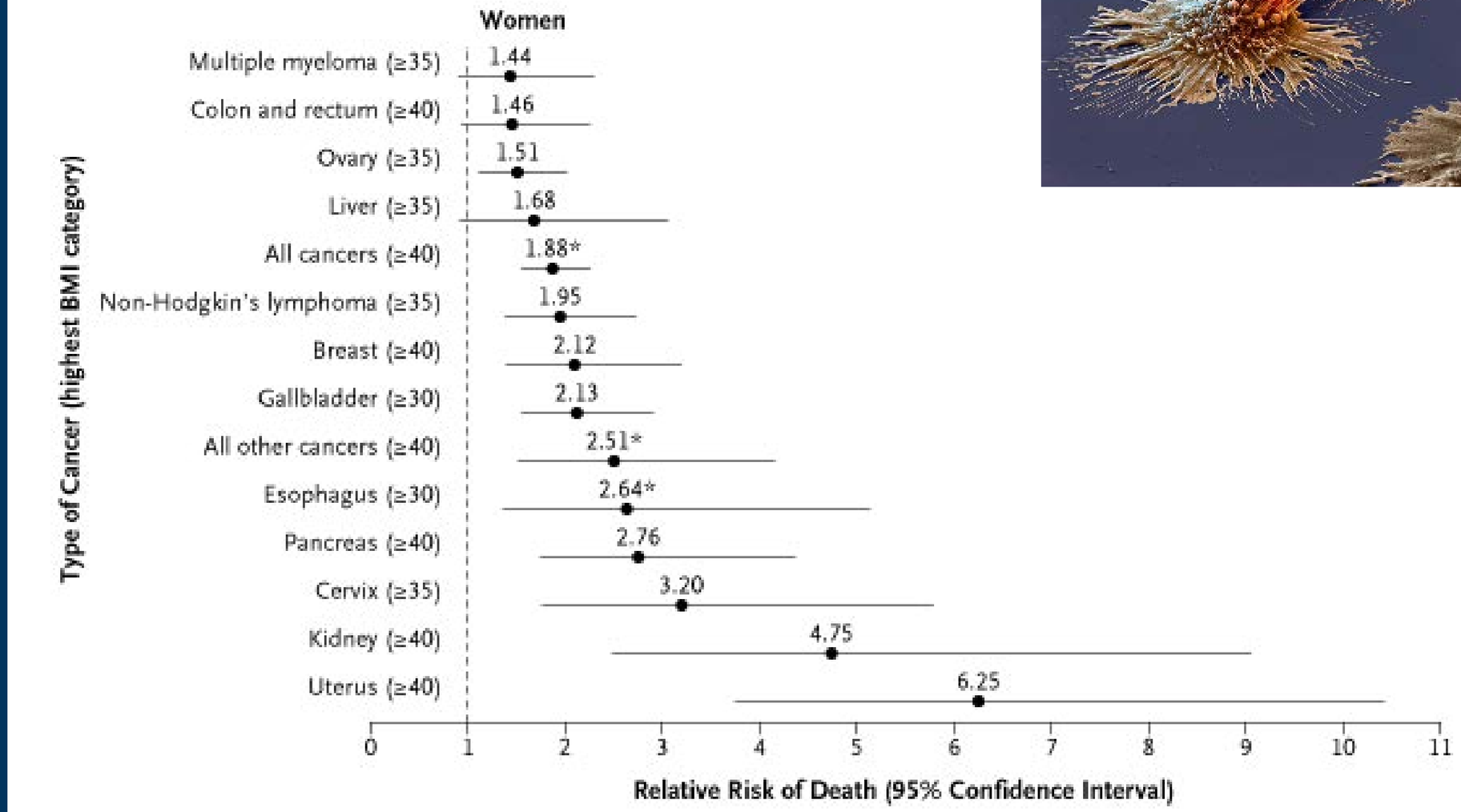
Obesity: Cancer
Men





Calle: NEJM (2003);348:17

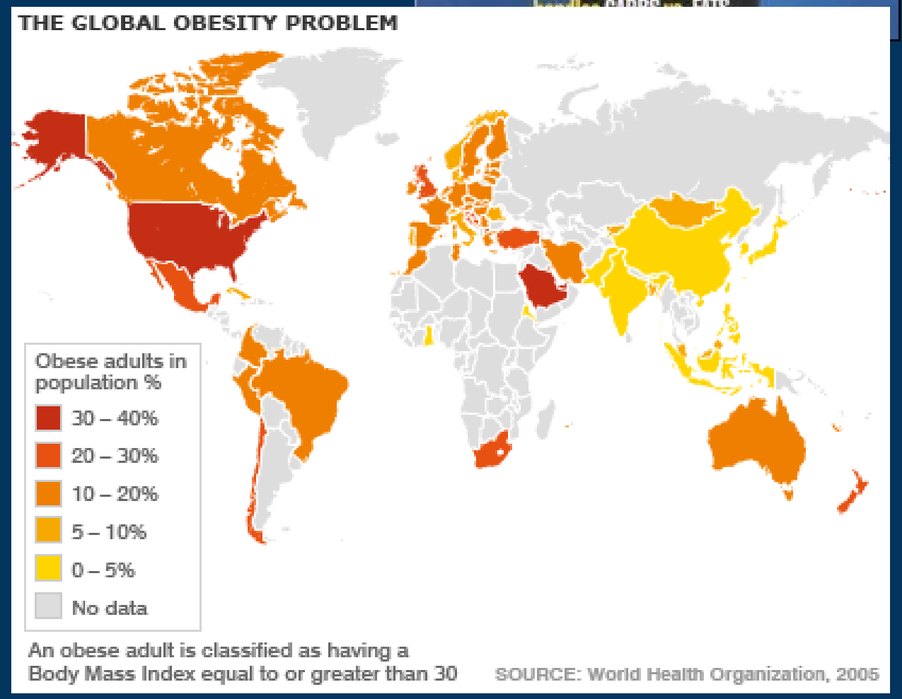
Obesity: Cancer Women



Calle: NEJM (2003);348:17

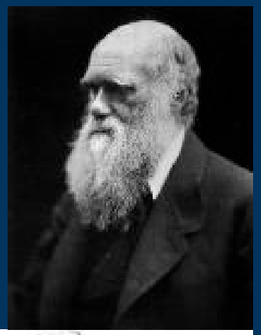
Etiology of Obesity: Genetics, Epigenetics or Environment ?

- Genetic inheritance
  - GWAS wt loss post bariatric surgery
- Environmental factors
- Socioeconomic issues
- Behavioral
- Psychological influences
- Cultural
- Microbiome changes
- GI Physiology
  - Altered gut derived signals
    - Gut hormones
    - Bile acids
    - Etc

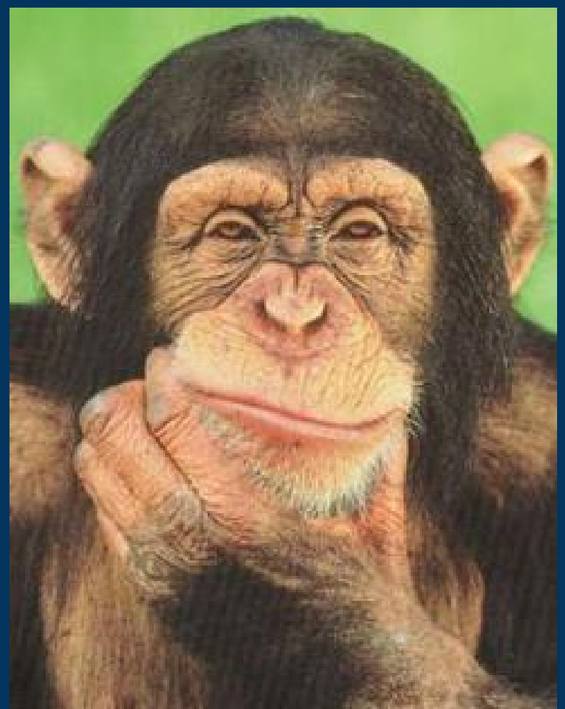


GWAS =Genome Wide Association Studies

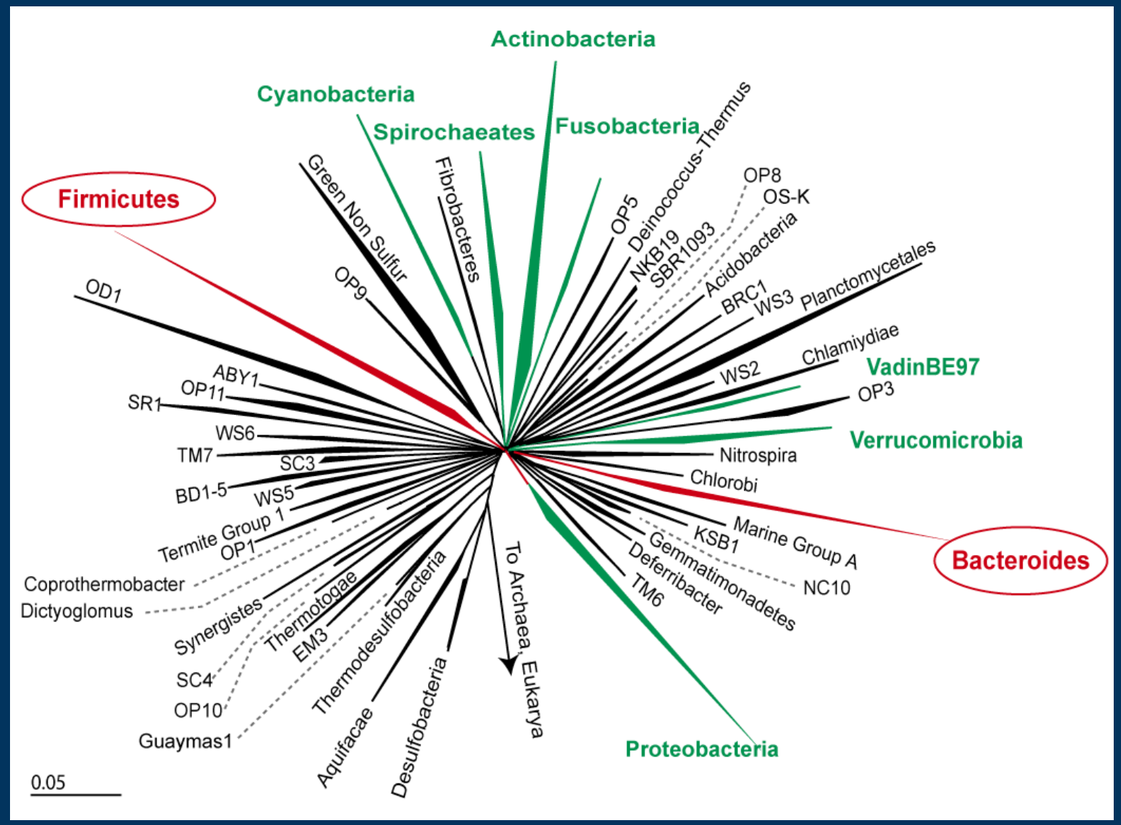
Man and Our Microbiome Continue to Evolve in "Darwinian" Fashion

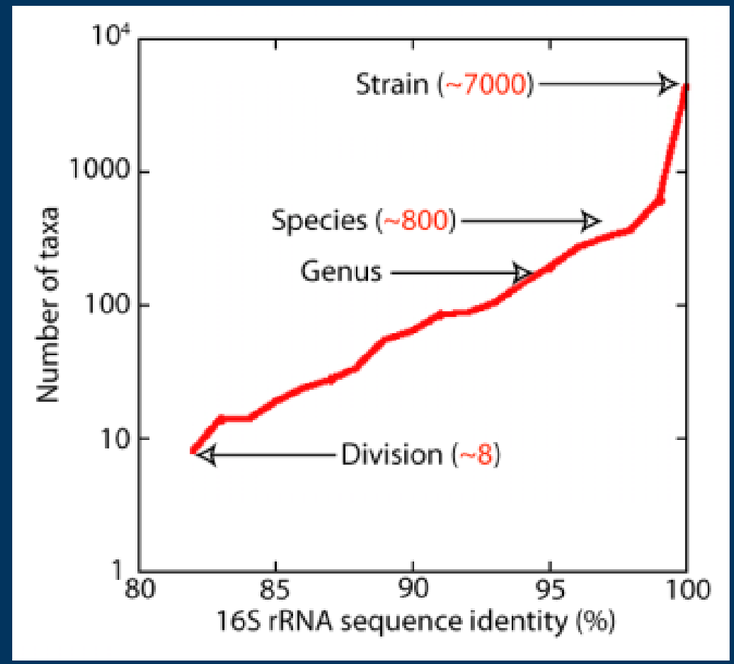


- Major dietary changes
  - Fats, protein, fiber, additives, sweeteners
- Changes in activity
  - Sedentary lifestyles
- Newborns in USA
  - 10 – 15 % CHO <u>for</u> microbiome
  - 1/3 c section, majority bottle fed
- Immunizations
- Decrease in parasitic infection
- Refrigeration
- Sanitation and hygiene standards
- Urban life in cities and concrete
- Increased use of antibiotics
  - Indicated or not !
  - collateral damage is real



Composition of the human gut microbiota



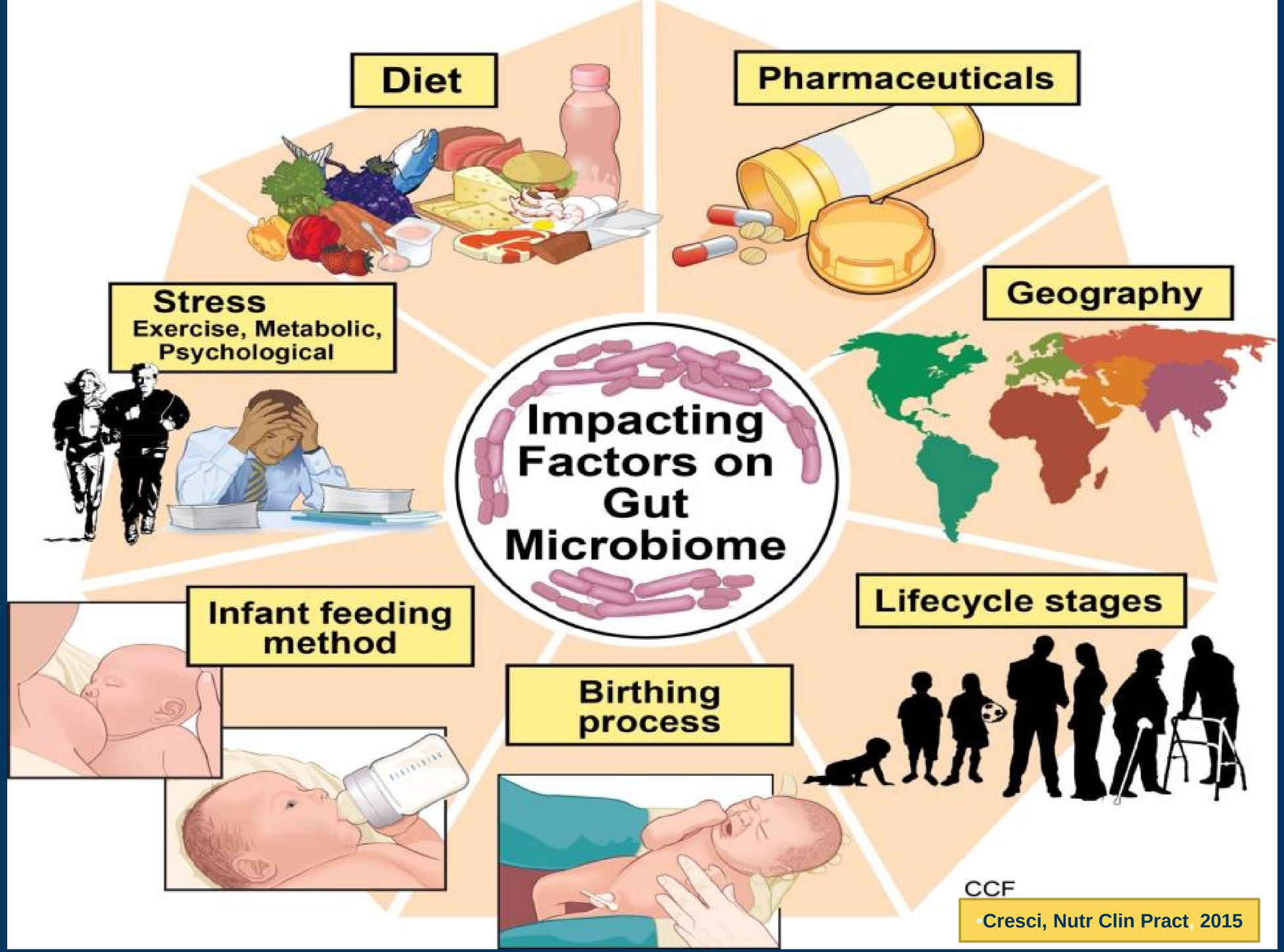


Only 9 bacterial divisions detected but note extreme diversity

Gut has strong selection for bacteria and redundancy of functions

- **Variety is thought to yield resilience to perturbations**

Bäckhed Science 2005

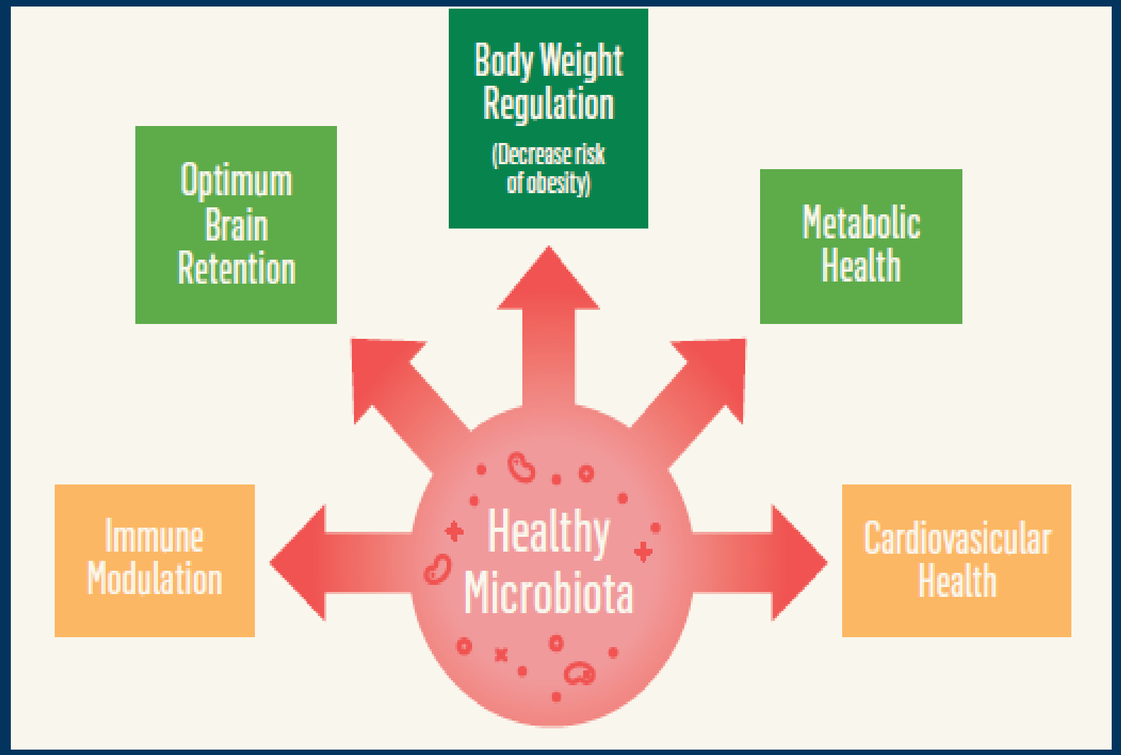


CCF

•Cresci, Nutr Clin Pract, 2015

Why care about gut bacteria?

- All eucaryotes have evolved in presence of bacteria.
- They surround us and we surround them !
  - Our immune system reacts to bacterial presence.
  - Bacteria produce metabolites and peptides.



Trophic

- Control of epithelial cell proliferation and differentiation
- Promote intestinal angiogenesis
- Development and homoeostasis of the immune system

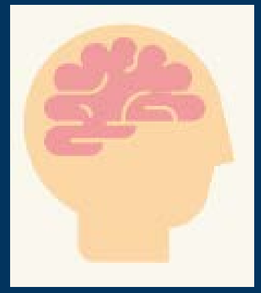
Protective

- Protection against pathogens

Metabolic

- Fermentation for SCFA
- Endogenous mucus
- Production of vitamin K
- Some AA, Neurotransmitters
- Xenobiotic metabolism
- Distant organ signaling

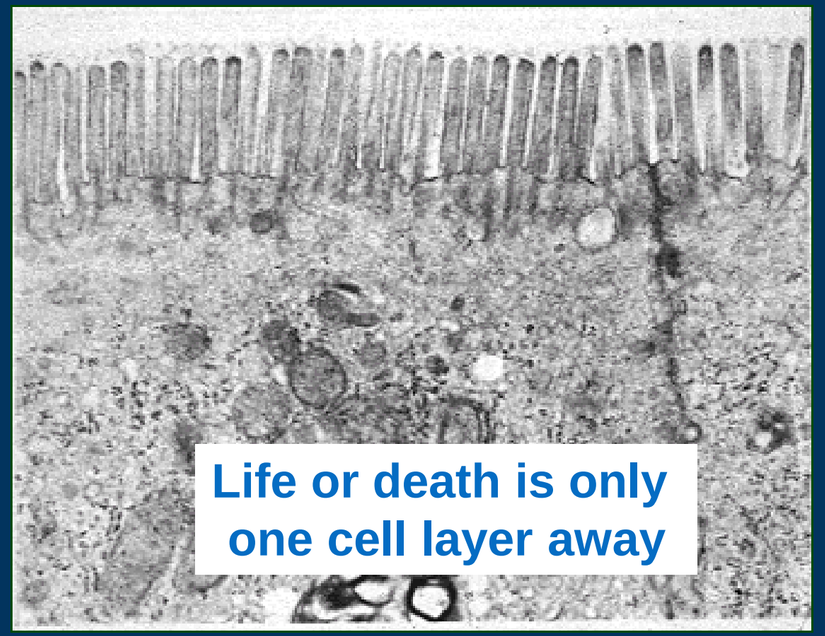
GI microbiota communication with peripheral organs



Organ	Process influences by gut microbiota	Disease associated with dysbiosis/microbial metabolites
Adipose tissue	Adipocyte volume Thermogenesis Browning Inflammation	Obesity/insulin resistance Insulin resistance
Liver	Bile acid metabolism Lipogenesis Energy expenditure	NAFLD/NASH
Pancreas	Insulin secretion	Type 2 diabetes
Whole body	Body growth	Undernourishment
Cardiovascular system		Stroke Atherosclerosis Thrombosis
Brain	Behavior Serotonin metabolism Intestinal gluconeogenesis Blood–brain barrier Appetite regulation	Autism spectrum disorder Stress response Metabolic disease
Lung	Gene expression	Allergic asthma

Schroeder BO, Backhed F. Nature Medicine 2016

Actions at the mucosal border: The Critical Balance !

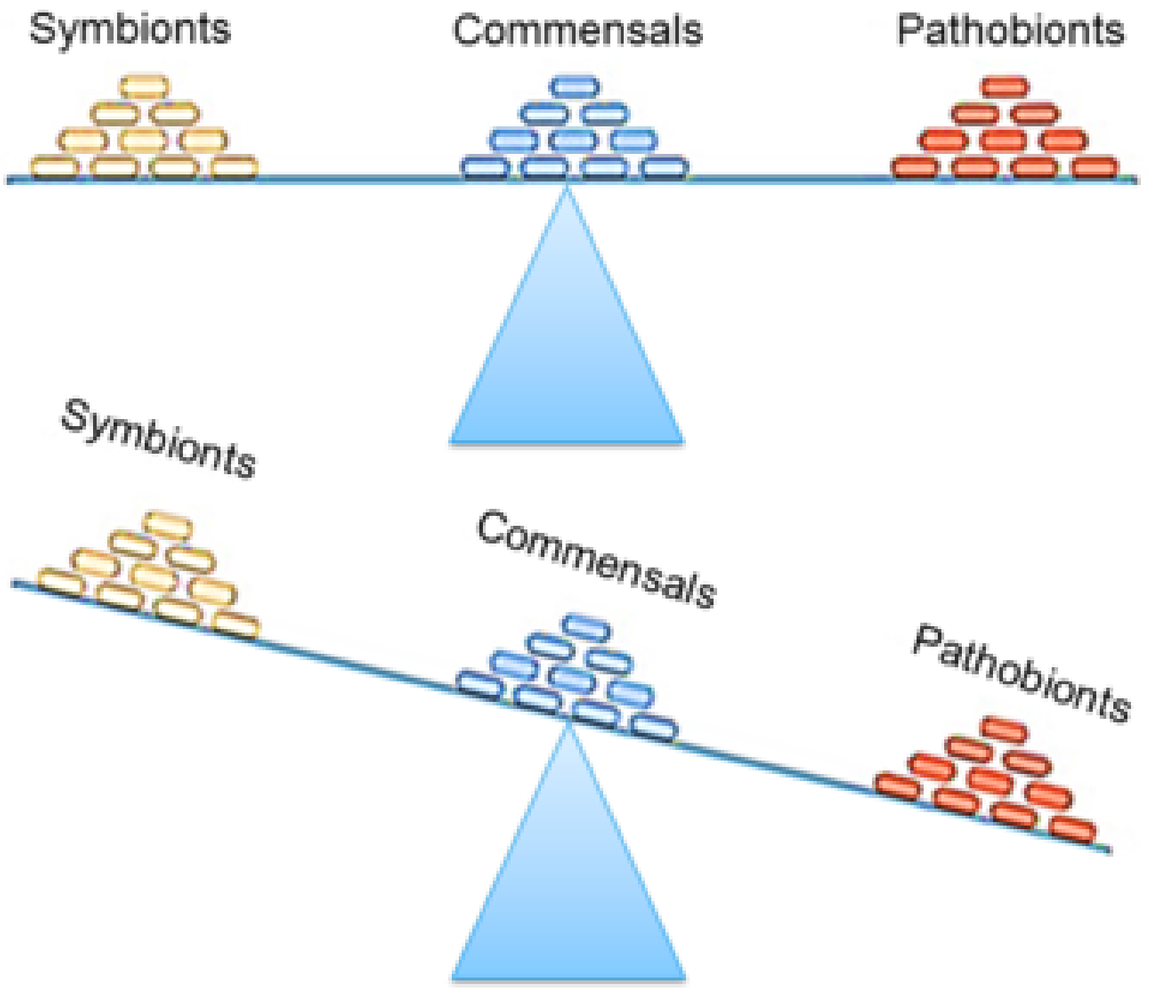


Fishman JE et al Ann Surg 2014
Ahmad R et al Nature Immunology 2016

Dysbiosis

Dysbiosis Defined

An alteration in the microbiome caused by a change in the composition of the microbiota, a change in microbial metabolic activity, and/or a shift in local distribution of communities of microbes.



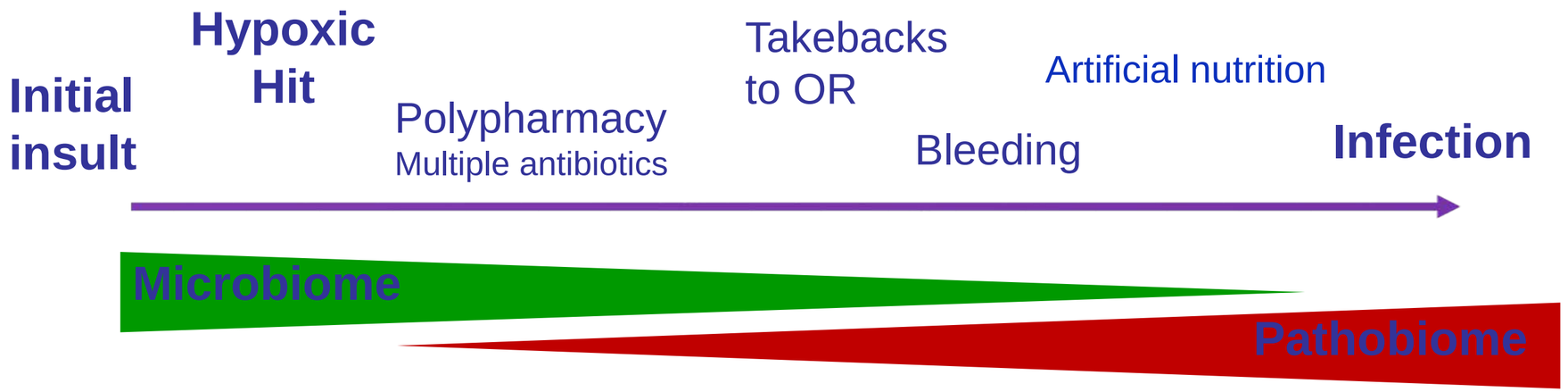
Round K:L et a;l Nature Rev Immunology 2009
Butto LF et al Int J Medical Micro 2016
Lin, L et al BMC Immunology 2017

The intestinal environment of surgical injury transforms *Pseudomonas aeruginosa* into a discrete hypervirulent morphotype capable of causing lethal peritonitis

Surgery
Volume 153, Number 1
2013

Trissa Babrowski, MD,[a] Kathleen Romanowski, MD,[a] David Fink, MD,[b] Moses Kim, MD,[a] Vissagan Gopalakrishnan,[c] Olga Zaborina, PhD,[a] *and* **John C. Alverdy, MD,[a]** *Chicago, IL, Boston, MA, and Baltimore, MD*

During critical illness, time is the enemy

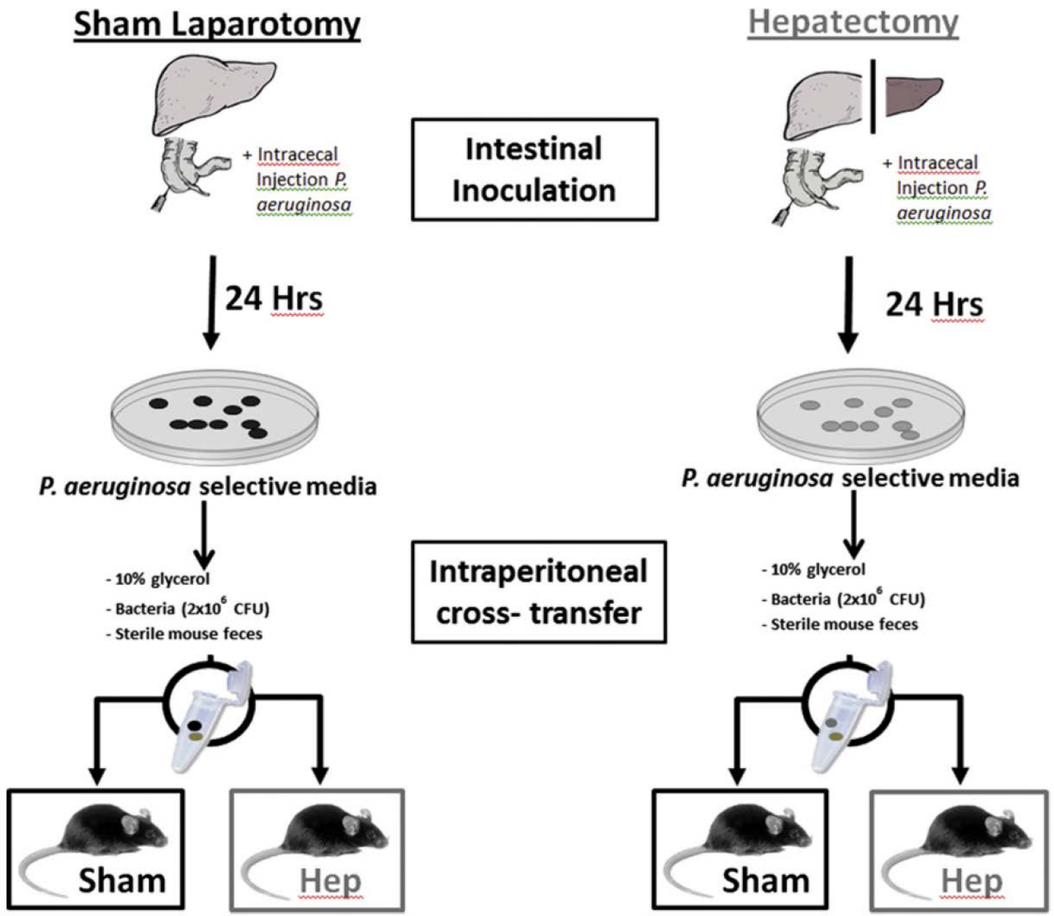


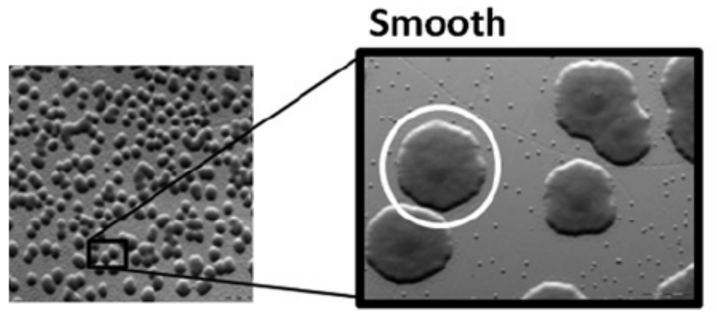
Critical loss of commensalism and the emergence of pathogens expressing enhanced virulence drives the immunopathology of critical illness

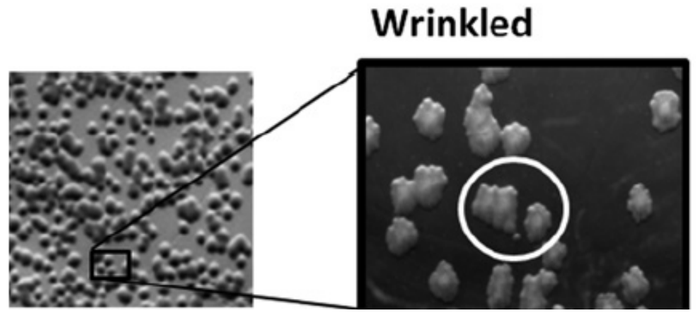
“Microbiome becomes Pathobiome”

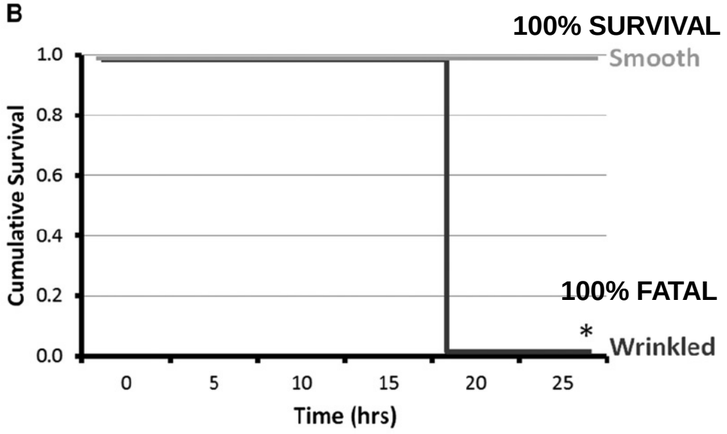
Guyton K, Alverdy JC et al Nature Rev GI 2016

Within 24 hours, a lethal *P. aeruginosa* morphotype develops









Microbial phenotype- NOT species, NOT immune background-caused death- so then what actually drives sepsis outcome?

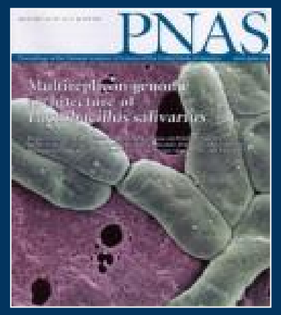
Delicate balance which surgery disrupts !

Clinical Application:
Microbiome literature: Science or Quackery ?

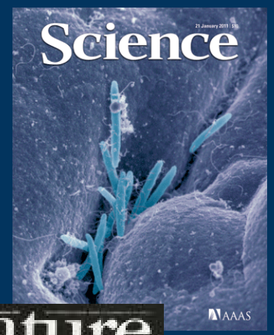
- **Professional Literature improving yet;**
  - Advanced techniques
  - Few ITT clinical studies available
  - Meta-analysis not consistent
- **Recent lead articles:**
  - PNAS 2016
  - Nature 2015
  - Science 2014
  - Wall Street Journal 2012
  - Scientific American 2012
  - Economist 2012
  - NY Times 2013

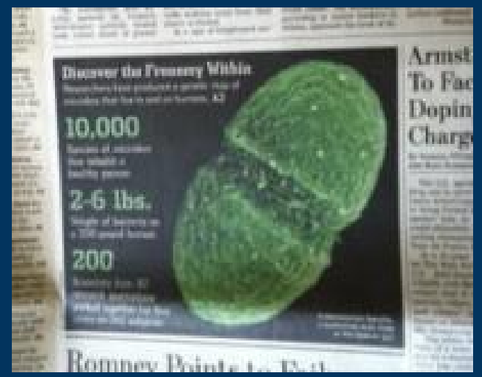
Skeptics view:

"….probiotics can't cure everything…."

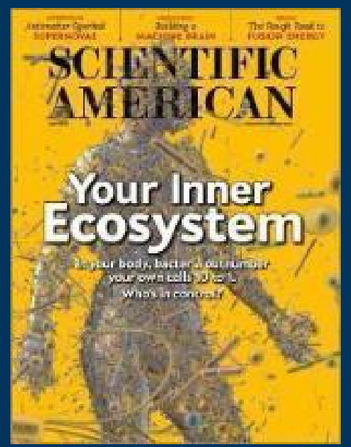


New York Times 2013



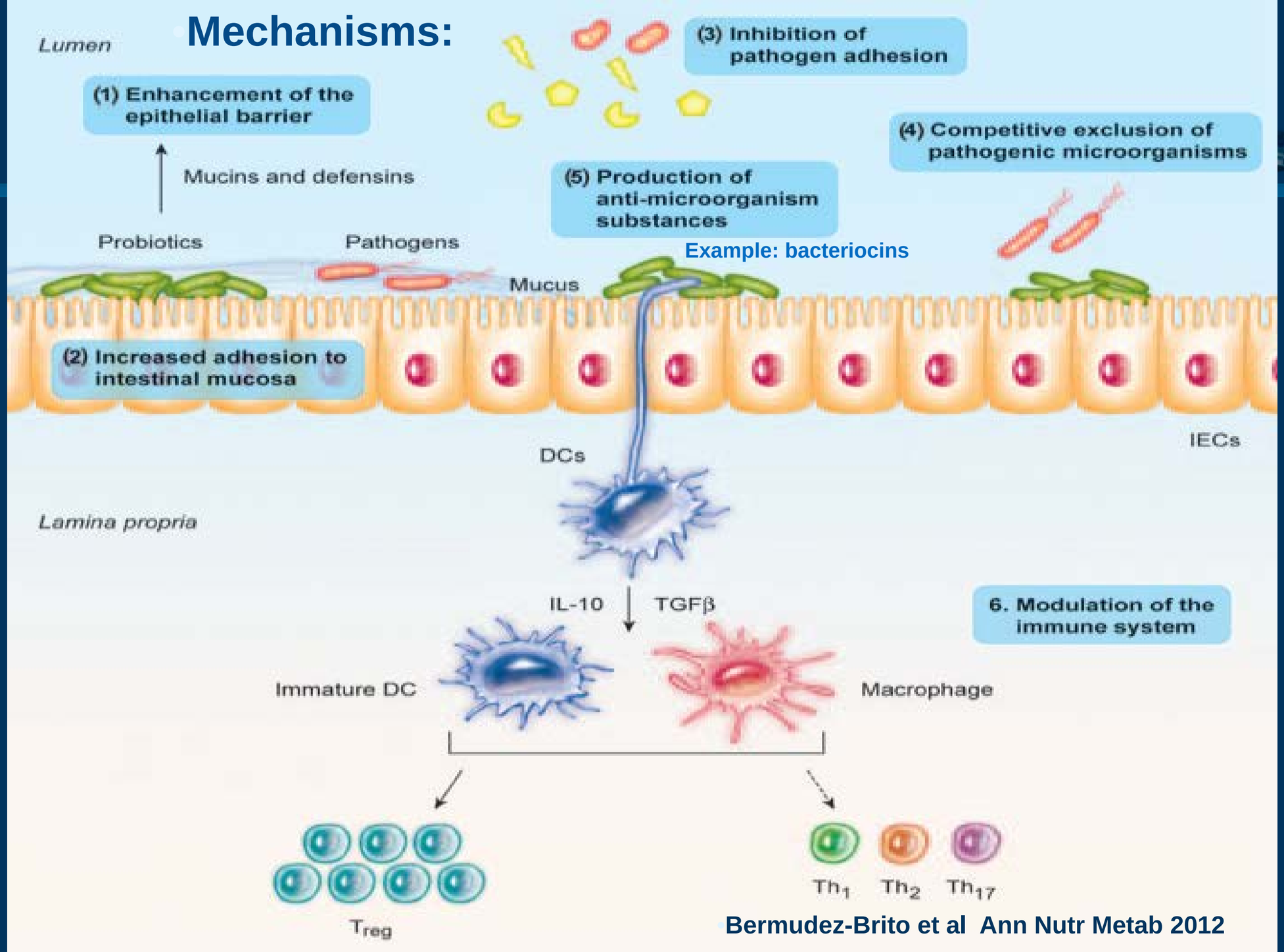


Wall Street Journal 2012

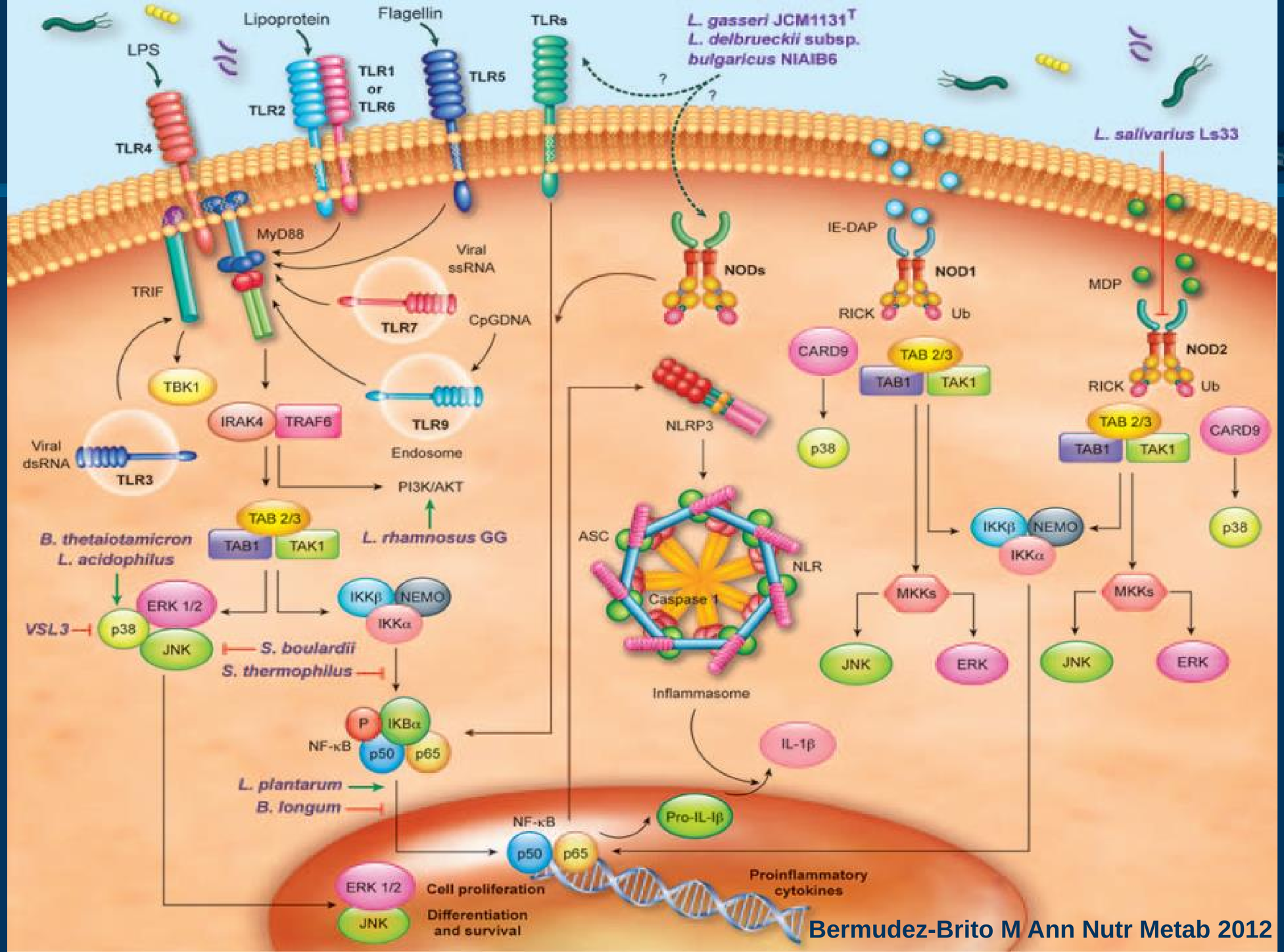


Has Our Fear of “Bacteria” Made Us More Susceptible to Disease

Mechanisms:



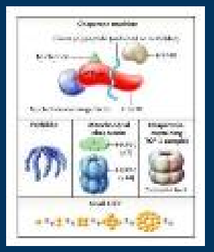
Bermudez-Brito et al Ann Nutr Metab 2012

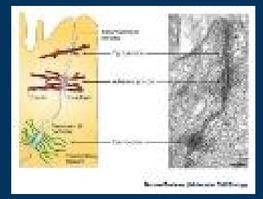


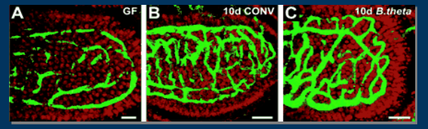
Bermudez-Brito M Ann Nutr Metab 2012

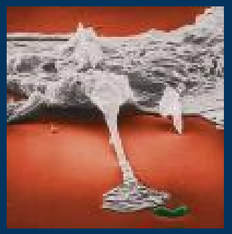
Multiple clinical mechanisms well described

- Competitive inhibition of pathogens
  - Alverdy data – GI anastomosis
- Enhance HSP in gut mucosa
- Tight junction protein synthesis
- Enhance mucosal blood flow
- Stimulate gut immunity
- Butyrate (fermentive end product) enhances neutrophil killing, chemotaxis, resolution of inflammation
- Butyrate- Anti-neoplastic activity
- Increases return of GI motility
- Helps maintains microbiome diversity in colon







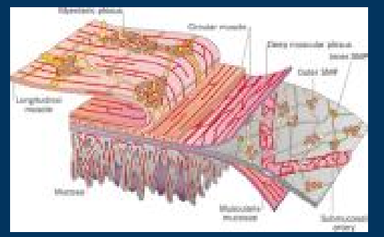


Additional mechanisms

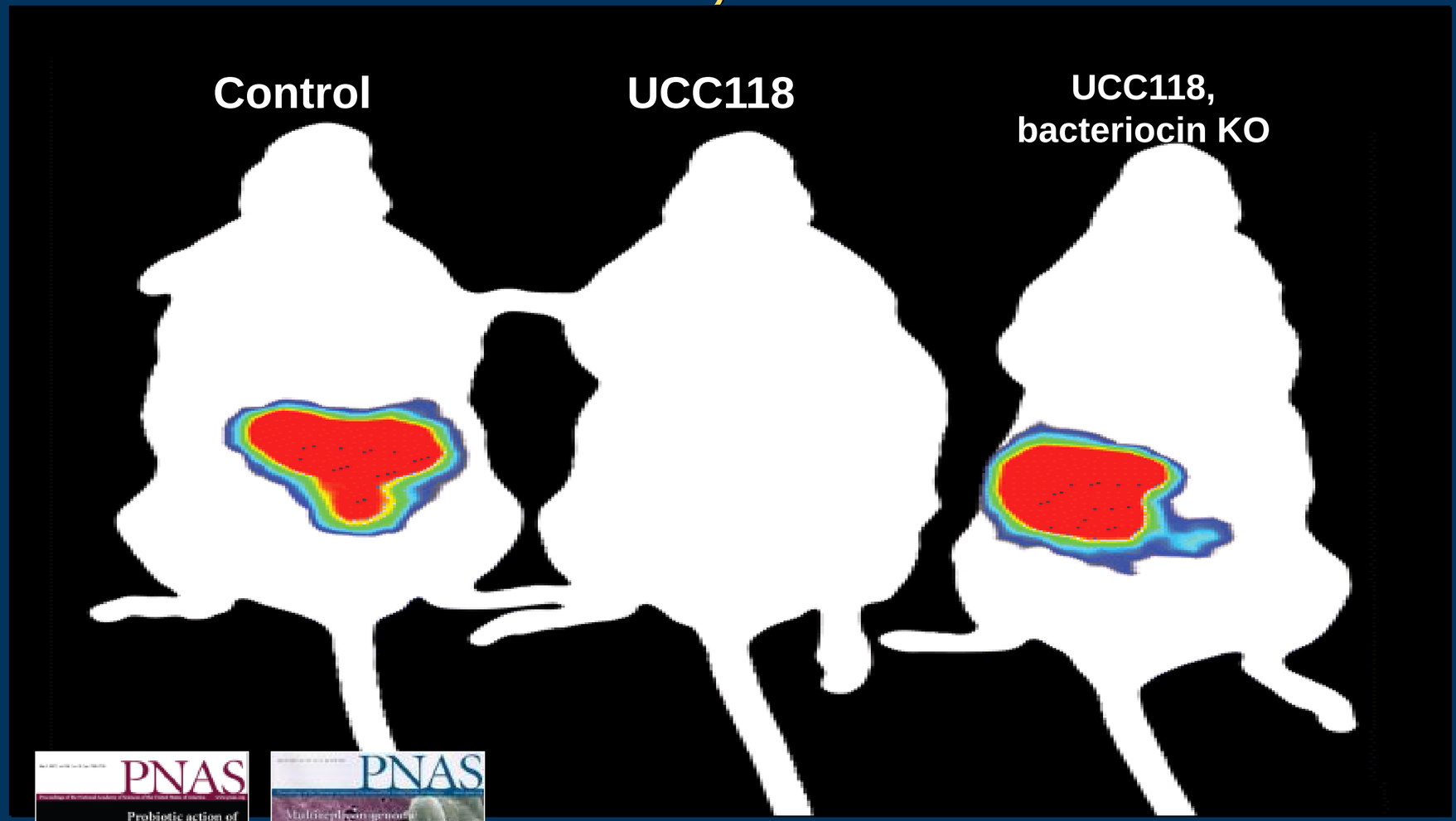
- Alterations in metabolism/energy utilization
  - Vitamin production in infant greatest effect (folate, B12)
  - Production and absorption of AA
- Bile salt hydroxylase – decrease fatty liver
- Microbiome activates Ca++ binding protein expression
- Interacts with ENS bidirectional communication
  - Nerve Growth Factor stimulated by Lactobacillus sp
  - Increases IL-10 which attenuates inflammation
  - Alters GABA in brain and shown to be anxiolytic
    - Blocked by vagotomy
  - Microbiome required for normal gut brain signaling

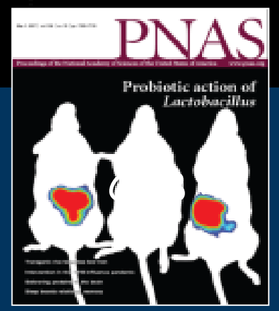
Bienenstock J et al Gut Microbes 2013

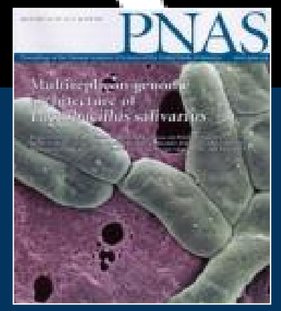
McVey-Neufeld KA et al Neurogastro and Motility 2015



L. *salivarius* (UCC118) prevents *Listeria* infection, in mice

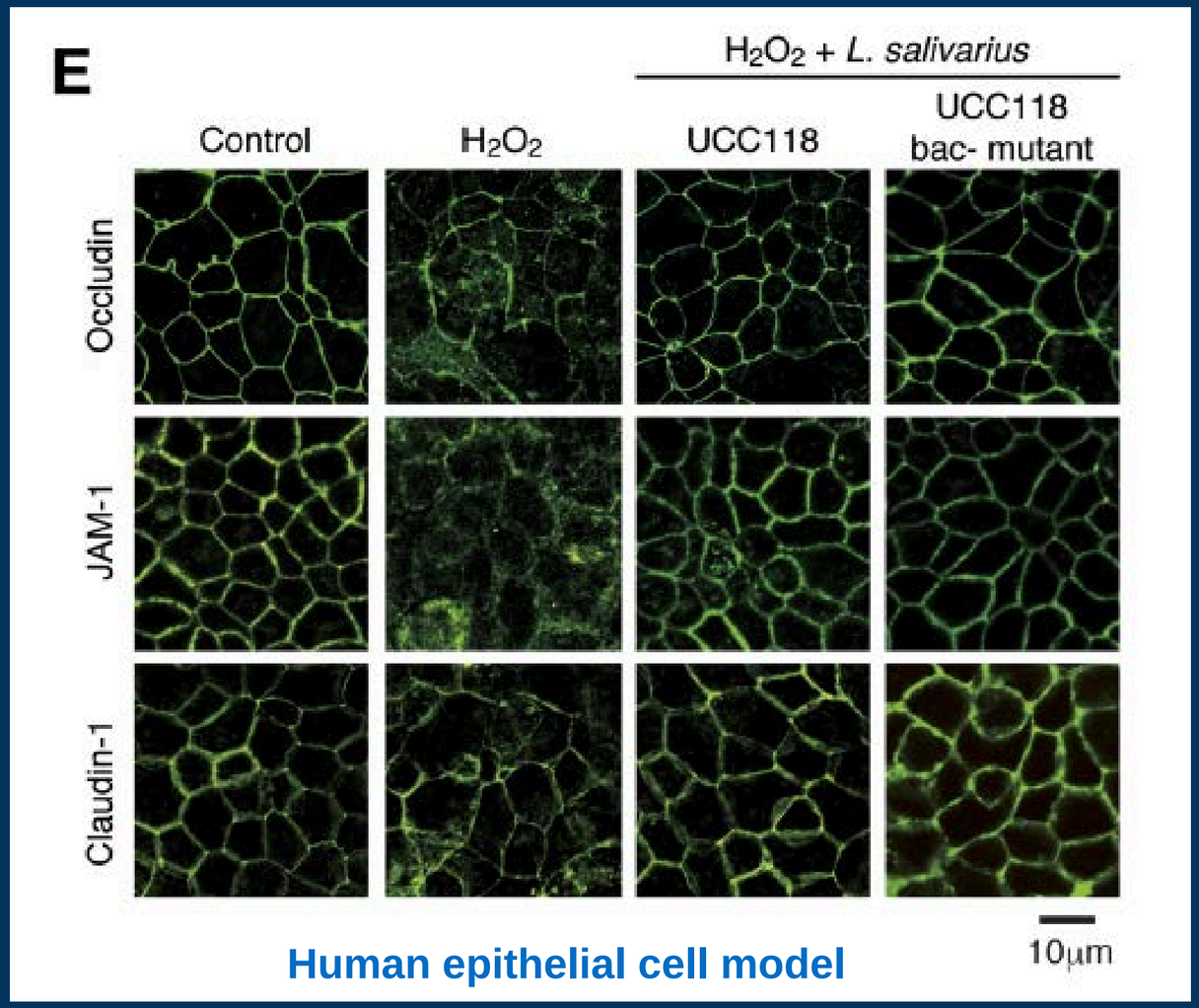




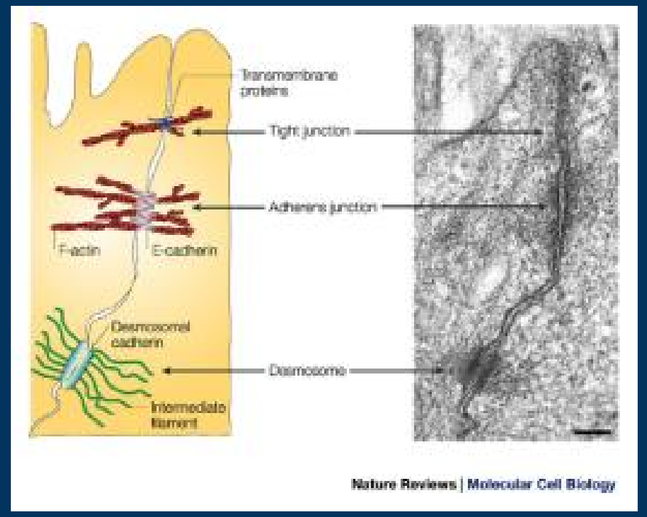


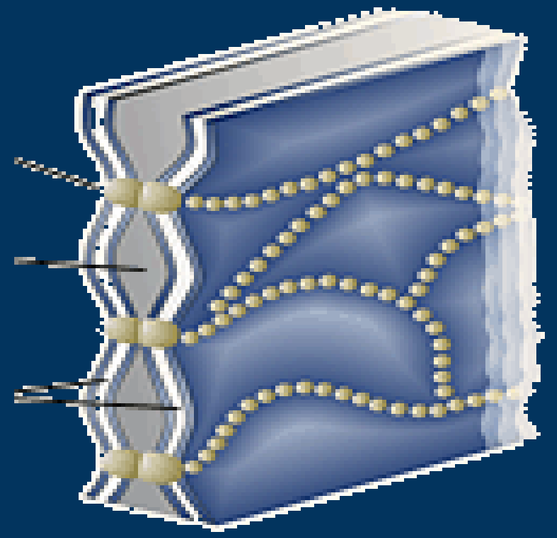
•Sinéad C. Corr, PNAS 2010

Lactobacillus *salivarius* (UCC118) prevents disruption of epithelial cell tight junctions



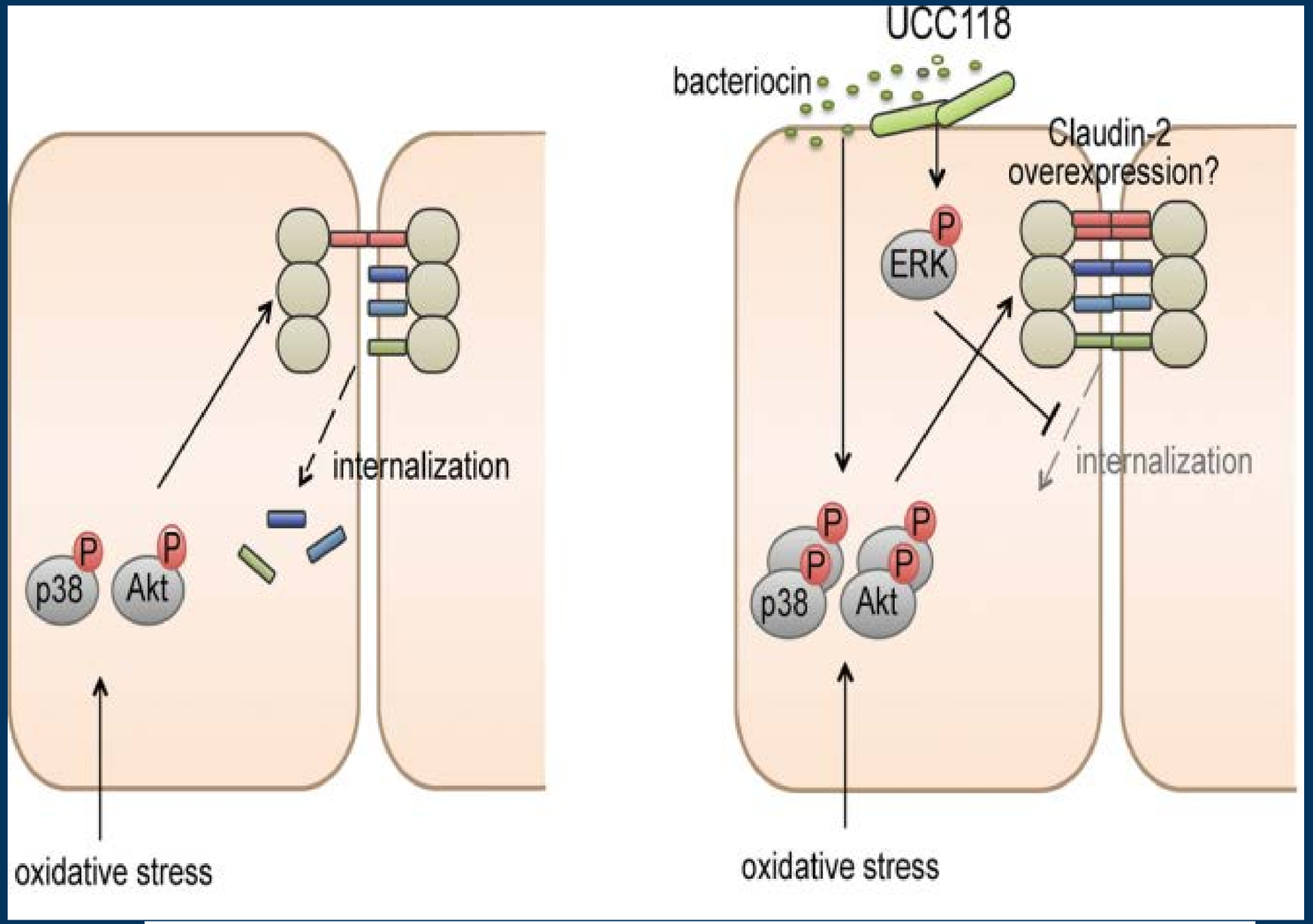
Human epithelial cell model





Miyauchi et al Am J Physiol Gastrointest Liver Physiol 2012

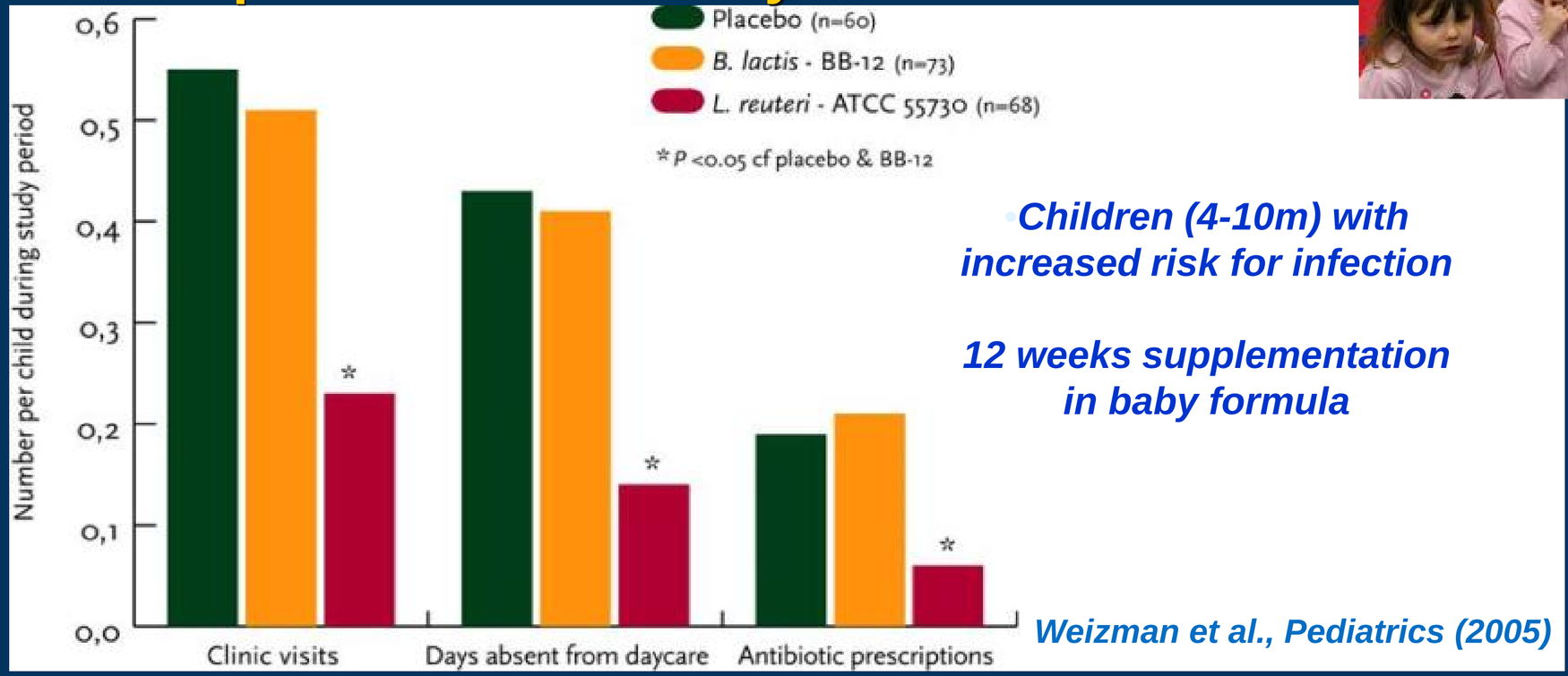
UCC118 alters tight junction protein localization.



Tight junction proteins

Pre and Probiotics:

Use probiotics in healthy school children



- ***Children (4-10m) with increased risk for infection***

- ***12 weeks supplementation in baby formula***

Weizman et al., Pediatrics (2005)

- **Saavedra JM et al 2004**
- PRDBPCT N=118, 3-24 months, 210 day
- +/- Probiotics
- **Results: Probiotic group**
  - **Decrease colic, antibiotic use**

- **Mugambi MN et al Nutr J 2012**
- Meta-analysis: Pre/Pro/Synbiotics, 25 studies total
- **Conclusion:**
- **No consistent high quality data to support;**
  - **Growth development, GI issues**

Lactobacillus rhamnosus GG Intake Modifies Preschool Children's Intestinal Microbiota, Alleviates Penicillin-Associated Changes, and Reduces Antibiotic Use

Katri Korpela[1]*, Anne Salonen[1], Lauri J. Virta[2], Minna Kumpu[3], Riina A. Kekkonen[3], Willem M. de Vos[1,4]

- **Results:**
  - **L. rhamnosus GG influences the composition of intestinal microbiome**
  - **Use prevents some of the changes associated with cephalosporin antibiotic use**
  - **Decrease in GI complaints**
  - **Treatment prevents subsequent infections up to 3 yrs**

Korpela K et al PLOS One 2016

Probiotics, Pregnancy and Maternal Outcomes

- Finland N=256 (3 groups)
- Strict definition of Gestational diabetes (GTT)
- Control, placebo, probiotics

- Results:
  - Control 36%
  - Placebo 34%
  - Probiotics 13%
  - No change in pregnancy outcome
  - No change in children at two years

Luoto R British J Nutrition 2010

- Systematic review: 189 articles
- Primary outcomes;
  - Gestational DM
- Secondary outcomes;
  - Pre-eclampsia
  - Inflammatory markers
  - Lipid profiles
  - Gestational weight
- Conclusion:Probiotics reduce
  - gestational DM
  - Maternal fasting glucose
  - Pre-eclampsia
  - CRP-inflammation

Lindsay KL et al 2013 J Maternal-Fetal Neonatal Med

Probiotics in the prevention of necrotizing enterocolitis in neonates

- 7% of VLBW < 1500 gm
  - 20 to 30% mortality
  - Etiology is clearly multifactorial
    - Premature birth, Abnormal intestinal microbiota
    - Enteral feeding , alterations in perfusion

- N=566 infants
  - 5 probiotic genera (4 bifidobacteria and 1 lactobacillus
    - 2 .0x 10^9 CFU /day
- Results
  - Reduction in Nec 9.8% vs 5.45 % (p<.05)
  - Reduction in Mortality 9.8 vs 6.8 % (NS)

Janvier A et al J Pediatrics 2014

Microbiome and Brain Development

- Gnotobiotic mouse model:
  - Substantially ↑↑ corticol response to stress
  - Decreased brain derived neurotrophic factors
    - Neurogensis, synaptic growth, synaptic plasticity altered
- Partially reversed by re-colonization with a normal mouse gut microbiota
- Suggests that active signals from the microbiota plays critical role in brain development and routine daily function
- Significant bidirectional communication
  - D-serine, GABA, Nerve growth factor
- Recent work with autism, anxiety, Alzheimer's, OCD, ADHD

O'Mahoney SM Neuroscience 2015

Bienenstock J et al Gut Microbes 2013

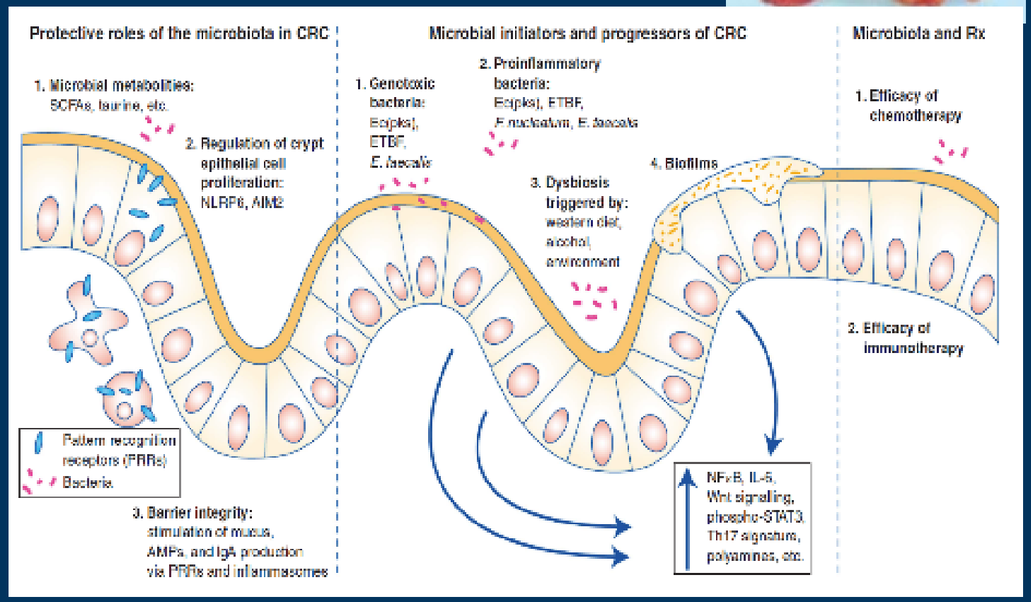
McVey-Neufeld KA et al Neurogastro and Motility 2015

Minter MR et al Sci Rep 2016

Ho P et al More Than a Gut Feeling 2017

Probiotics in the prevention, treatment and management of Colorectal Cancer

- **Microbiome**
  - Key to sporadic colon Ca



- **New data – microbiome changes during tx CRC**
  - Microbiome alters chemotherapeutic agents to enhance immune host immune function
  - **“drugs need bugs”**
  - Probiotics partially protective from effects of chemo and radiation

Azcarate-Peril MA et al. Am J Physiol (GI Liver Physiol) 2011
Ciobra MA et al Gut 2012 (radiation)___Viaud S et al Sci 2013
Bordon Y et al Nature Rev Immunology 2014___Demers M et al Clin Nutr 2014
Yang Y et al European J Clin Nutr 2016___Drewes JL Sears CL Brit J Ca 2016

A Four-Probiotics Regimen Reduces Postoperative Complications After Colorectal Surgery: A Randomized, Double-Blind, Placebo-Controlled Study

June 2015 World J Surg

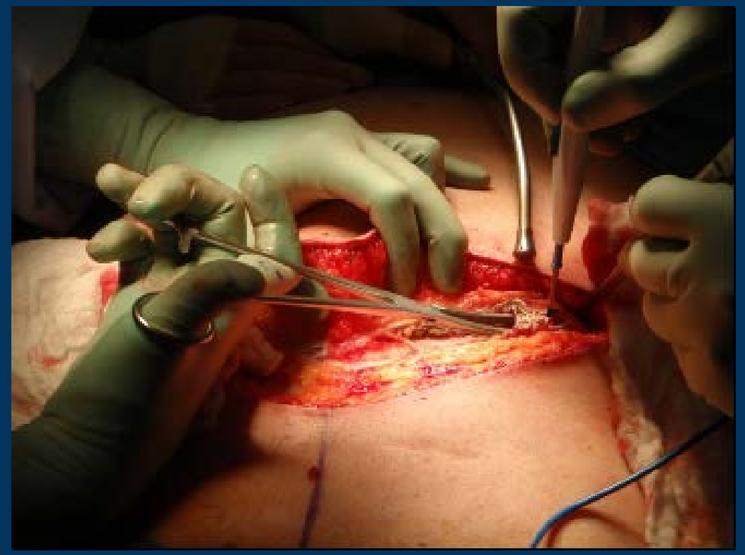
Katerina Kotzampassi[1] · George Stavrou[1] · Georgia Damoraki[2] · Marianna Georgitsi[2] · George Basdanis[1] · Georgia Tsaousi[1] · Evangelos J. Giamarellos-Bourboulis[2]

- **Design:**
  - PRCT Placebo Controlled double blind
  - Colorectal Cancer N=146
- **Methods:**
  - 4 probiotics vs placebo
    - » L.acidophilus, L.plantarum, B.lactis, Saccharmyces boulardii
  - Given one day before surgery and then 15 days after
- **Results:**
  - Decrease pneumonia (2.4 % vs 11.3%)
  - Decrease SSI (7.1% vs 20.0%)
  - Decrease anastomotic leak (1.2%vs 8.8%)

Probiotics and synbiotics for the prevention of postoperative infections following abdominal surgery: a systematic review and meta-analysis of randomized controlled trials

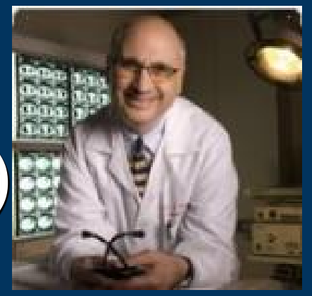
L. Lytvyn [a, b], K. Quach [a], L. Banfield [c], B.C. Johnston [a, b, d, e], D. Mertz [a, f, g, h, *]

- **20 trials, N=1374 patients**
- **Conclusions:**
  - **Decrease**
    - **SSI**
    - **UTI**
    - **Total infections**
  - **No increase adverse events**
  - **No change in mortality**



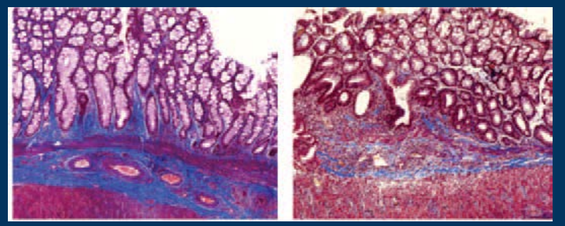
Lytvyn L et al J Hosp Infections 2016

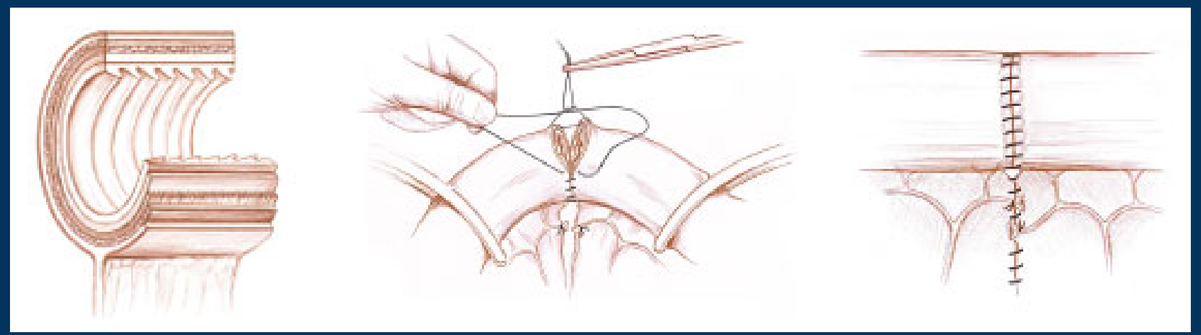
Prevention of GI Anastomosis failure



- Animal and human models (John Alverdy's group)
  - Pseudomonas, enterococcus after anastomosis
    - Expression of barrier disrupting MMP9, PA-IL, etc
- Bacteria at sight of anastomosis change phenotype and become more aggressive and produce toxic metabolites and enzymes(MMP9) which increase risk of anastomotic disruption
    - Altered by MBP, antibiotic bowel prep, ischemia etc

Early data showing a "healthy" microbiome will limit anastomotic leaks





Fink D, et al J Trauma 2011
Morowitz MJ et al Ann Surg 2011
Stern JR et al J Surg Res 2013
Shogan, BD et al J GI Surg 2013
Shogan BD et al Microbiome 2014
Shogan BD et al Science 2016

Probiotics and Synbiotics Decrease Postoperative Sepsis in Elective Gastrointestinal Surgical Patients: a Meta-Analysis

Sudha Arumugam[1] · Christine S. M. Lau[1,3] · Ronald S. Chamberlain[1,2,3]

J. GI Surg 2016

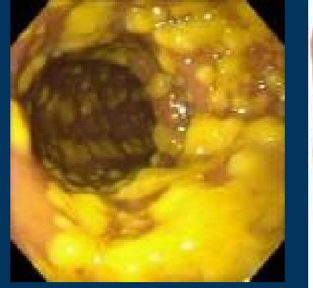
- **Introduction:**
  - 751,000 incidence of sepsis episodes in USA / yr
  - $22,000 / episode, $16 billion annually
  - Mortality 15 to 30%
- **Methods:**
  - 1966-2015
  - Sepsis within one month of surgery
- **Results:**
  - 15 RCT, 1201 patients
  - 192 probiotics, 413 synbiotics and 596 placebo
  - Decrease in post op sepsis with pro/synbiotics by 38%
    - (Relative risk .62, 95% CI, p<.001)

Antibiotic Associated Diarrhea: Preventable or Inevitable ?

- Hempel S et al JAMA 2012
- Meta-analysis 82 RCT met criteria for inclusion
- Probiotics strains were poorly documented
- N=11,811 participants (pooled data)
- Conclusion:
  - Probiotics confer significant decrease in AAD ($p<.001$)
  - # needed to treat N=13

Hempel S et al JAMA 2012

Use of probiotic preparations to prevent C.difficile Associated Diarrhea



- RDBPCT N=135
- Age 64 all taking antibiotics
- 100 gm BID L. casei as drink
- Results:
  - AAD: 7/57 (12%) vs 19/56 (34%)
  - 21% relative risk reduction, NNT 5
  - C.diff 0/57 vs 9/53 (17%)

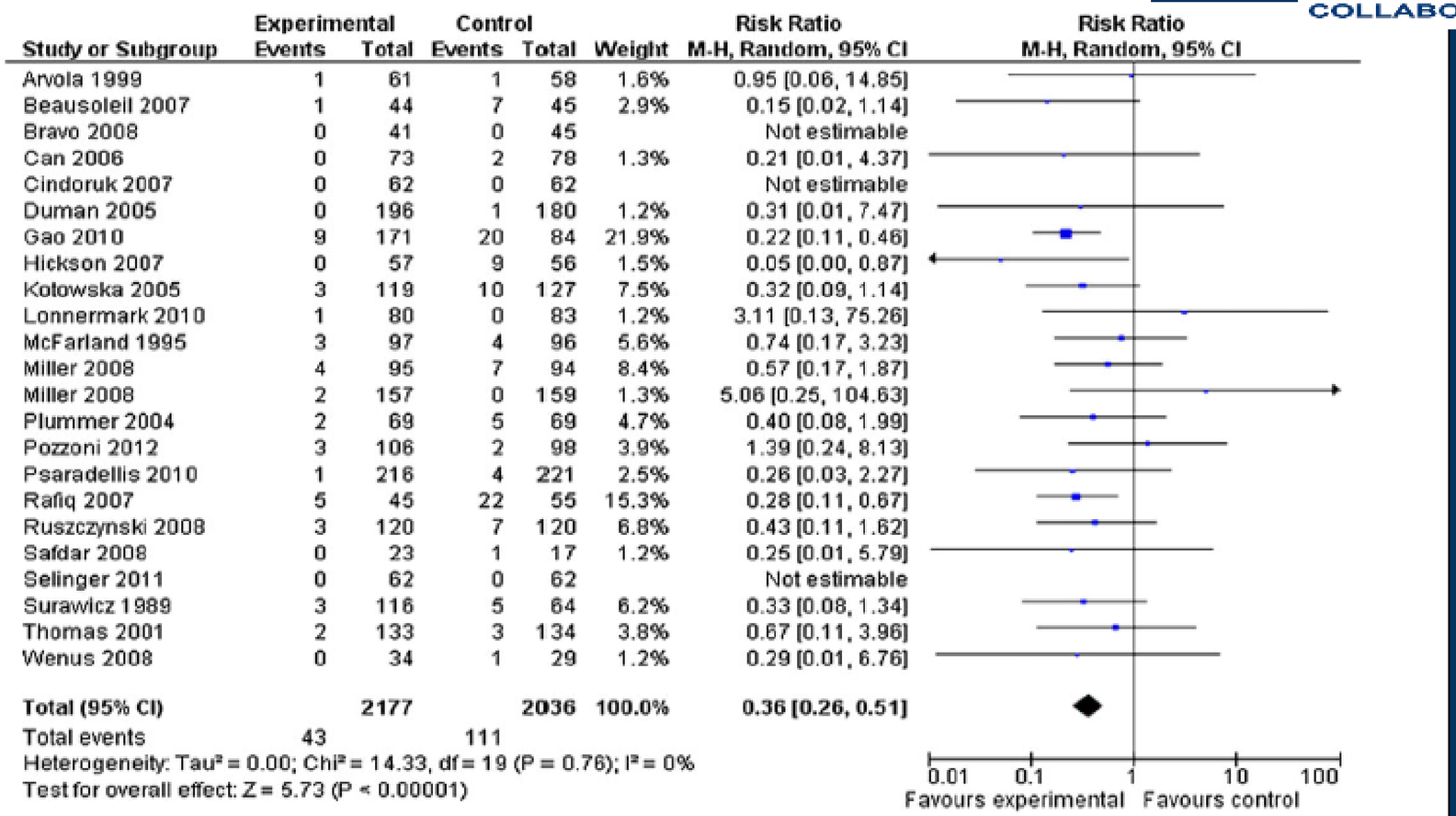
Hickson M, et al . BMJ 2007

- Meta-analysis 28 studies
- N=3818 patients

- "Moderate quality" of evidence probiotics as prophylaxis
  - decreases incidence of CDAD by 66%
  - No adverse influence by receiving probiotics

Johnston BC Ann Internal Medicine 2012

Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children (Review)



Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Arvola 1999	1	61	1	58	1.6%	0.95 [0.06, 14.85]
Beausoleil 2007	1	44	7	45	2.9%	0.15 [0.02, 1.14]
Bravo 2008	0	41	0	45		Not estimable
Can 2006	0	73	2	78	1.3%	0.21 [0.01, 4.37]
Cindoruk 2007	0	62	0	62		Not estimable
Duman 2005	0	196	1	180	1.2%	0.31 [0.01, 7.47]
Gao 2010	9	171	20	84	21.9%	0.22 [0.11, 0.46]
Hickson 2007	0	57	9	56	1.5%	0.05 [0.00, 0.87]
Kotowska 2005	3	119	10	127	7.5%	0.32 [0.09, 1.14]
Lonnermark 2010	1	80	0	83	1.2%	3.11 [0.13, 75.26]
McFarland 1995	3	97	4	96	5.6%	0.74 [0.17, 3.23]
Miller 2008	4	95	7	94	8.4%	0.57 [0.17, 1.87]
Miller 2008	2	157	0	159	1.3%	5.06 [0.25, 104.63]
Plummer 2004	2	69	5	69	4.7%	0.40 [0.08, 1.99]
Pozzoni 2012	3	106	2	98	3.9%	1.39 [0.24, 8.13]
Psaradellis 2010	1	216	4	221	2.5%	0.26 [0.03, 2.27]
Rafiq 2007	5	45	22	55	15.3%	0.28 [0.11, 0.67]
Ruszczynski 2008	3	120	7	120	6.8%	0.43 [0.11, 1.62]
Safdar 2008	0	23	1	17	1.2%	0.25 [0.01, 5.79]
Selinger 2011	0	62	0	62		Not estimable
Surawicz 1989	3	116	5	64	6.2%	0.33 [0.08, 1.34]
Thomas 2001	2	133	3	134	3.8%	0.67 [0.11, 3.96]
Wenus 2008	0	34	1	29	1.2%	0.29 [0.01, 6.76]
Total (95% CI)		**2177**		**2036**	**100.0%**	**0.36 [0.26, 0.51]**
Total events	43		111			

Heterogeneity: Tau² = 0.00; Chi² = 14.33, df = 19 (P = 0.76); I² = 0%
Test for overall effect: Z = 5.73 (P < 0.00001)

Figure 3. Meta-analysis of prevention of *Clostridium difficile* infection from Cochrane review 2013 [7]. Abbreviations: CI, confidence interval; M-H, Mantel–Haenszel.

23 studies
4213 patients

- **For CDI - RR – 0.89 (0.64 – 1.24)**
- **RR – 0.36 (0.26 – 0.51)**

Goldenberg et al. Cochrane Database Syst Rev. 2013.

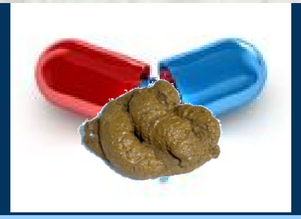
The ultimate microbiome delivery: Is stool from a "good friend" or family member the answer for refractory C. *difficile* diarrhea

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

- RTC 39 patients with proven refractory C. *difficle*
- 16 got Donor feces / 13 received QID vancomycin
- Results:
  - Feces group
    - 13/16 resolved with single infusion
    - 2/3 resolved with second infusion
  - Vancomycin group
    - 4/13 resolved

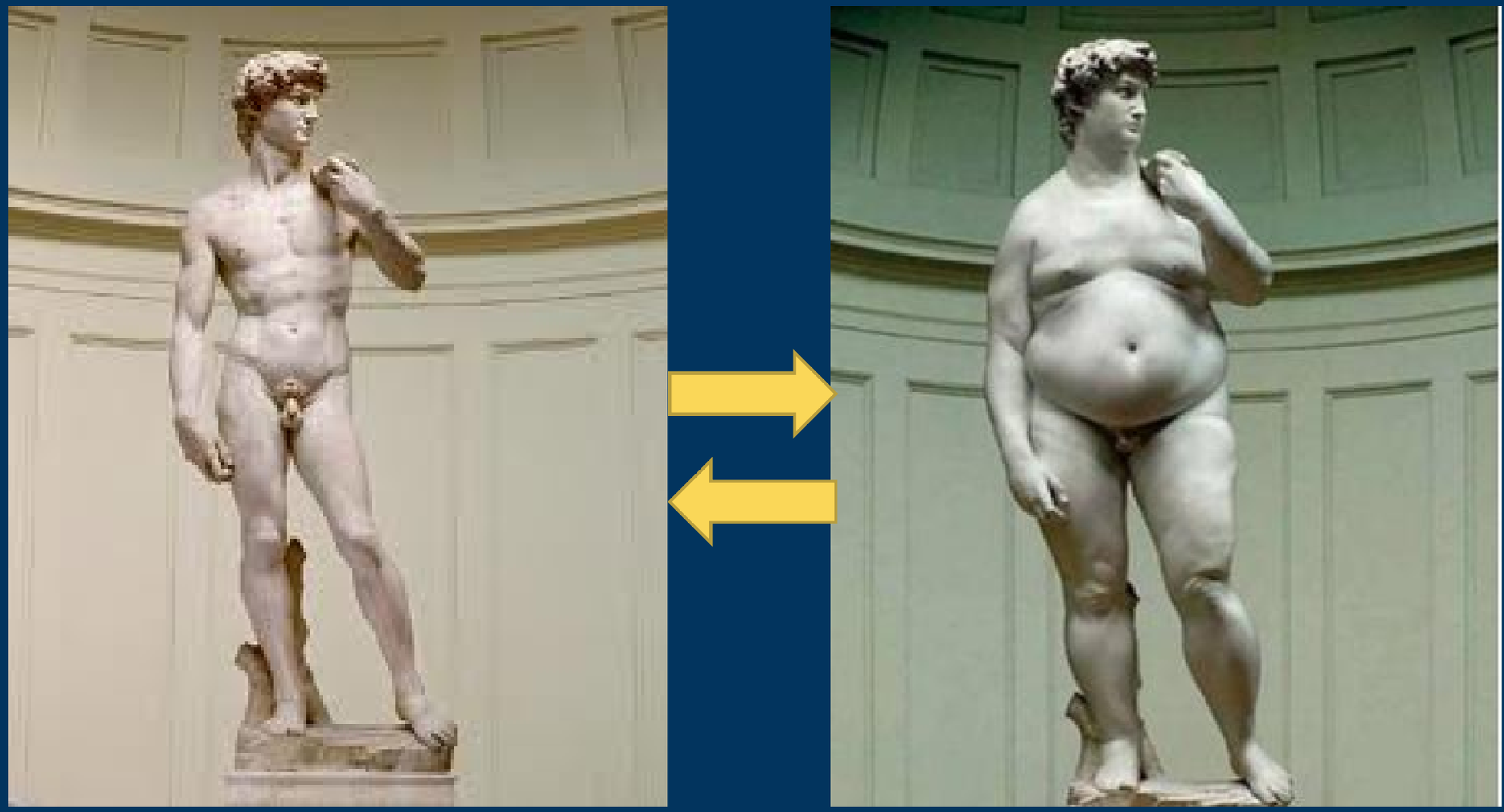


Nood EV NEJM 2013

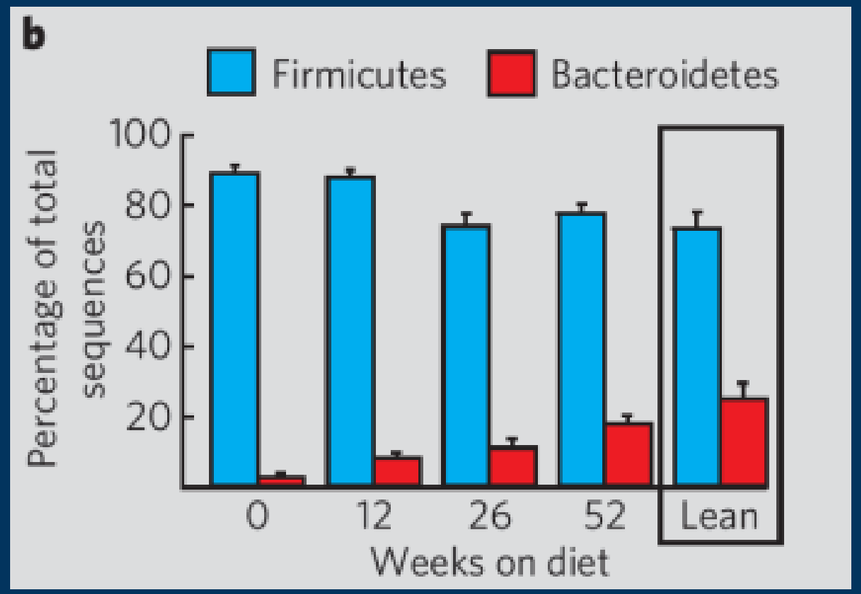
Hamilton MJ et al
Frozen "fecal" prep for C.*diff*
43 consecutive, recurrent CDI
95% success
Am J Gastroenterology 2012

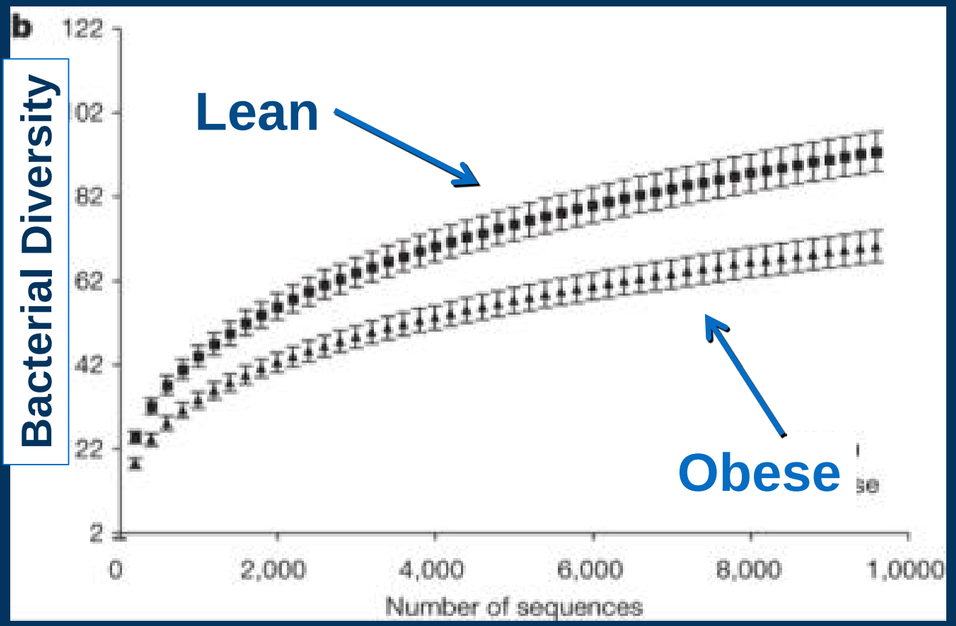
Konturek PC et al J Physio Pharma 2015

Could manipulation of the “Microbiome” help with weight control *or* be responsible for obesity ?



Reduced diversity of the gut microbiota in obese individuals

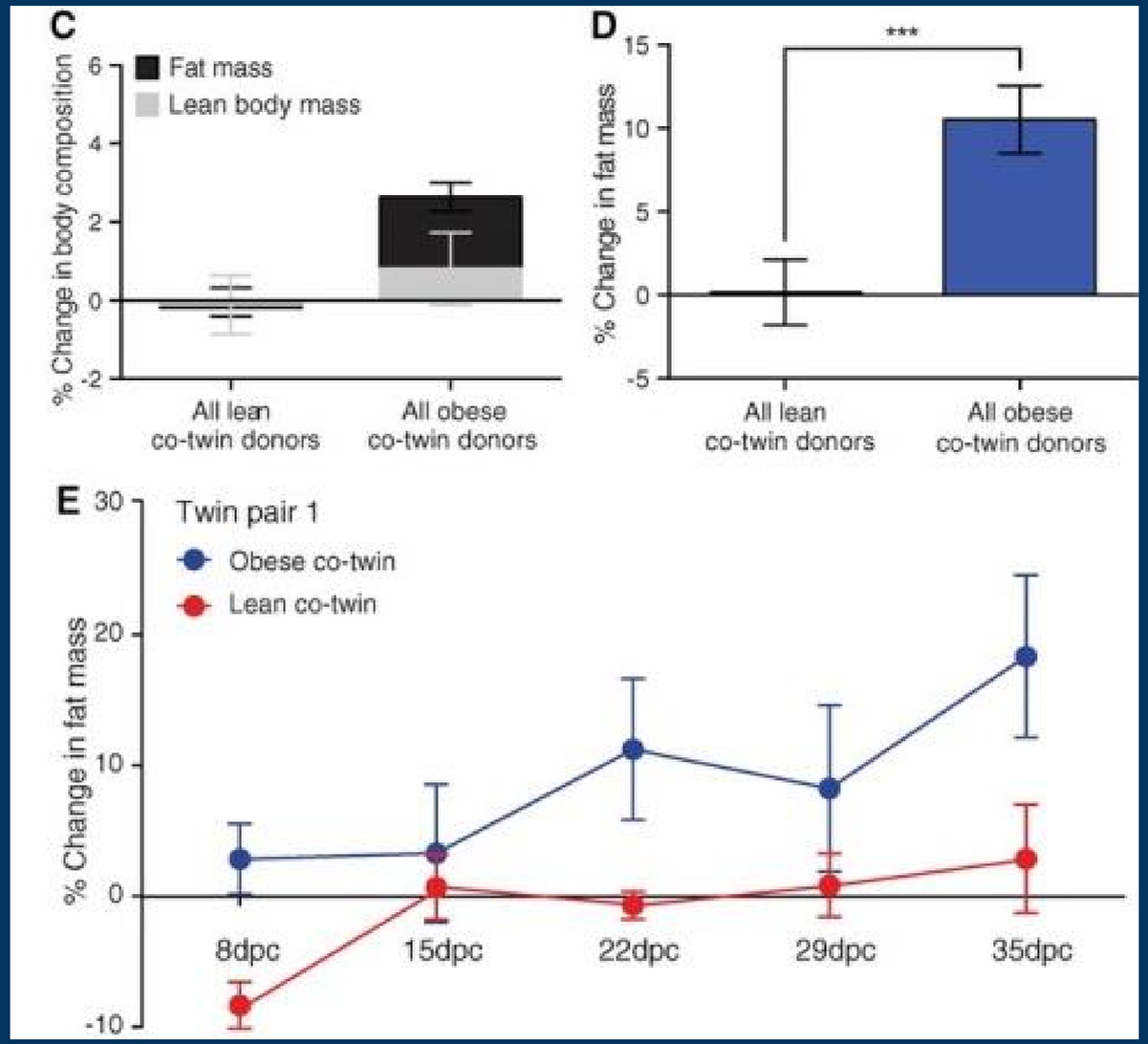




Large inter individual variation in flora composition but trends are consistent between multiple trials

- Ley et al. Nature 2006
- Turnabugh et al. Nature 2009

Human obesity is transplantable

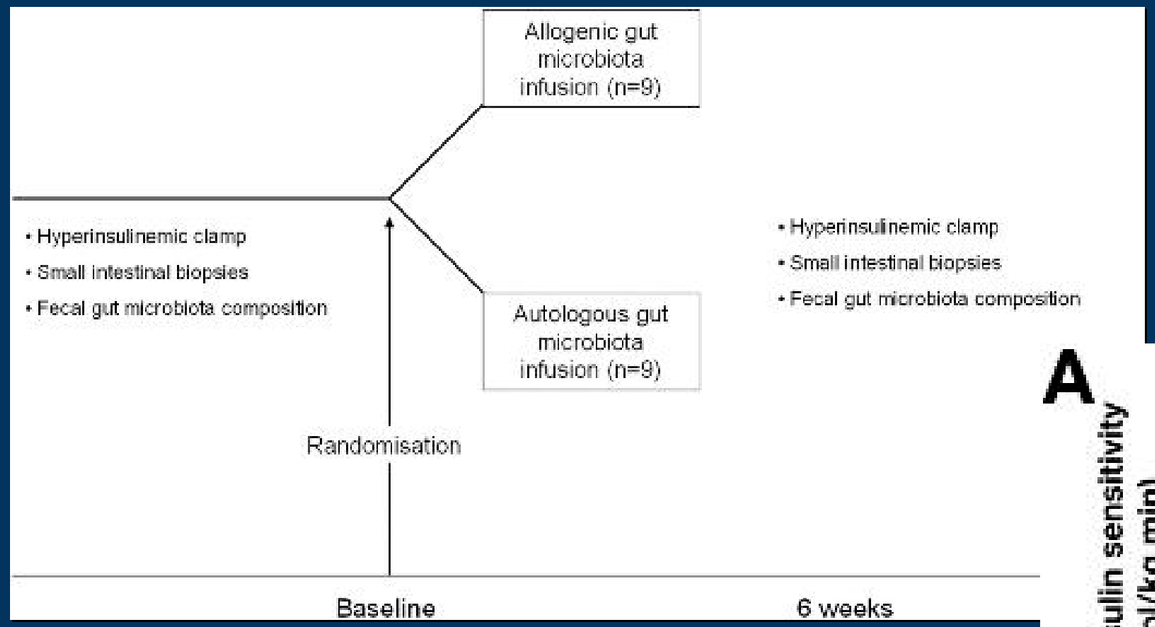


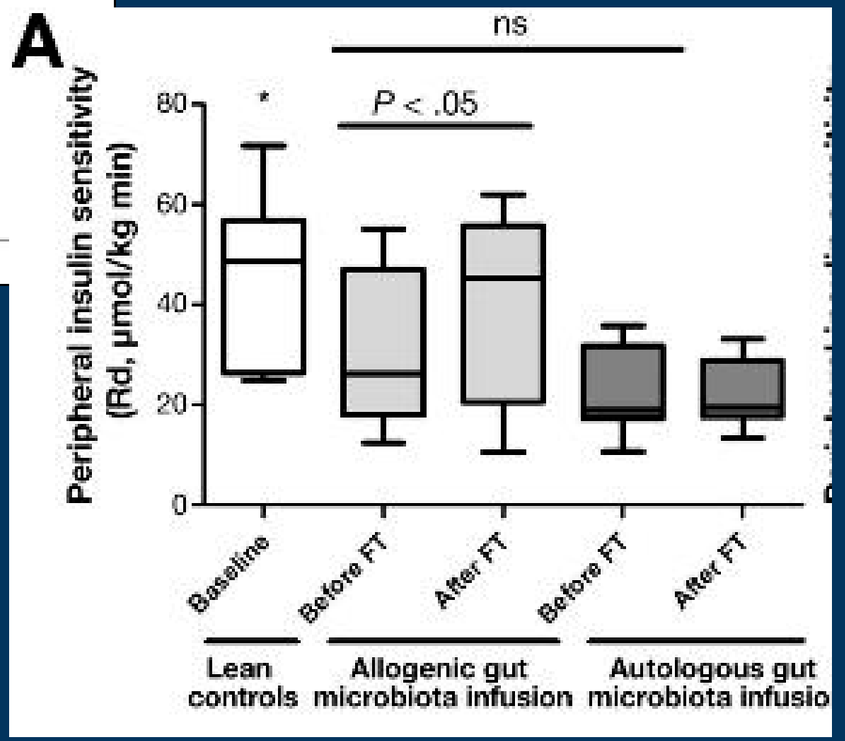
Transplantation of flora from twins discordant for obesity into germ-free mice show causal effect of microbiota.

Ridaula et al.Science 2013

Insulin Sensitivity is Transplantable

Gut microbiota in T2DM





Gut microbiota affects insulin sensitivity in humans

Vrieze A et al. Gastroenterology 2012

Current Problems with “Probiotic”

- Extravagant claims without data
  - Still perceived as “quackery” by many
- ? of good manufacturing practice
  - Quality assurance
    - » Additional species and devoid of label common
  - Label vs content
  - Viabilty of bacterial species
    - » Strain variation, SNP changes ?
- Validate biomarkers for assessing function and activity
- Improve the reliability and ease of taxonomic classification of pre and probiotic
  - Culture independent methods
  - Fermentation index
  - FISH (fluorescent in situ hybridization)
  - 16S ribosomal amplification and sequencing techniques
  - Pulse-field gel electrophoresis
  - Amplified fragment-length typing, terminal restriction polymorphism
  - Multi-locus sequence typing
- No specific guidelines currently
  - USA far behind EU in regulation

Sanders ME Ann NY Acad Sci 2011

Where do prebiotics fit in to the attempt to beneficially alter the microbiome ?

Fermentable Fibers: Benefits for the General Population

- Immune regulation – SCFA, multiple others
- Gastrointestinal motility
- Serves as agent for detoxification agent
- Large reproducible observation studies to show:
  - Decrease risk of type 2 DM and obesity
    - » 57% of T2DM resulting from obesity
  - Decrease risk of Coronary artery disease
  - Decrease Cancer (primarily visceral Ca)
  - Recent data on benefit in OCD, ADHD (altering microbiome)
    - » Animal models of Alzheimer's show improvement
- Decrease in all cause <u>mortality</u>

Zong G et al Circulation 2016
Makarem N et al Nutr Rev 2016
Obata Y et al Gastroenterology 2016
Wang J et al Nature Med 2015
Winer DA et al Cell Metab 2016
Keiffer DA et al Adv Nutrition 2016

Whole Grains

- BMJ June 2016
  - Aune D et al
  - 45 studies
  - Decrease in all cause mortality
  - Modest amounts
    - 3 serving per day
- Circulation June 2016
  - Zong G et al
  - Prospective cohort studies 786,076 participants
  - Whole grains
    - Decrease all cause mortality
      - CVD, Ca, etc

Prebiotics

- Three necessary criteria of ingredient
  - Non-digestible by host enzymes
  - Fermented in GI tract
  - Selective stimulation of gut microbiota and metabolic activity
  - Demonstration of criterion is difficult
- A prebiotic is not available to all bacterial species that inhabit GI ecosystem
  - *Lactobacillus* and *Bifidobacterium* considered indicator organisms
- Naturally occurring or synthetic sugars, starches
  - Used as a carbon source by certain colonic bacteria for growth and metabolism
  - Examples: Inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), lactulose
- Breast milk the ultimate prebiotic solution
    - 15% of CHO in breast milk is prebiotic

Breast Milk Felt to be the “Perfect F

- Nutrient rich
  - Modulates colonization and development of immature newborn gut
- Functional carbohydrate
  - Not absorbed by child
  - Ferments in the distal bowel
- Probiotics also present
  - Found via culture and non-culture techniques
  - Streptococcus 91%
  - Staphyloccus 83%
  - Entero-mammary pathway

Nutrition Facts
Breast milk

Amount Per 1 cup (246 g)			
Calories 171			
			% Daily Value*
Total Fat 11 g			16%
Saturated fat 4.9 g			24%
Polyunsaturated fat 1.2 g			
Monounsaturated fat 4.1 g			
Cholesterol 34 mg			11%
Sodium 42 mg			1%
Potassium 125 mg			3%
Total Carbohydrate 17 g			5%
Dietary fiber 0 g			0%
Sugar 17 g			
Protein 2.5 g			5%
Vitamin A	10%	Vitamin C	20%
Calcium	7%	Iron	0%
Vitamin D	1%	Vitamin B-6	0%
Vitamin B-12	1%	Magnesium	1%

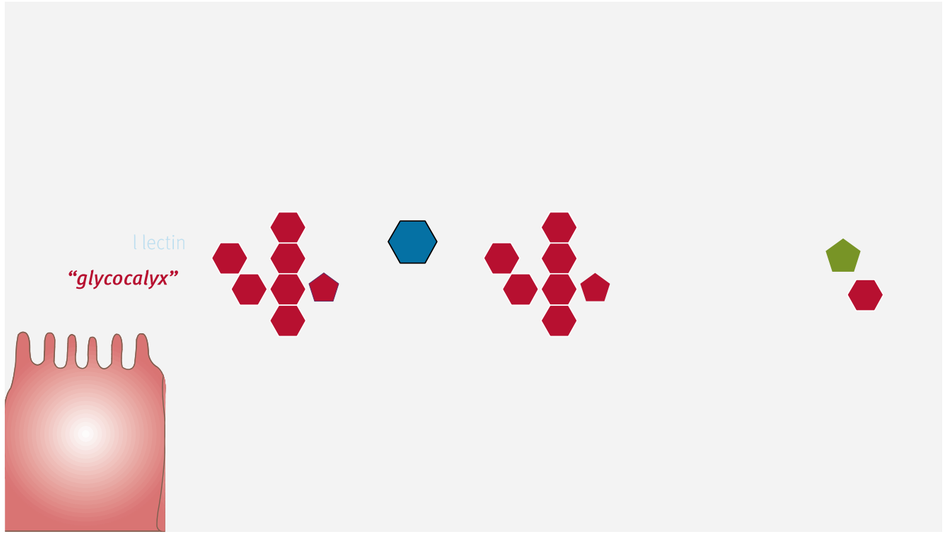
*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.

•Fitzstevens JL et al NCP 2016

What are Human Milk Oligosaccharides (HMOs)?

"take the gut back to where it began"

- **200 unique carbohydrate structures have been identified in human milk**
  - **Make up ~ 15% of total CHO**
  - **2'Fucosyllatctose is the most abundant** HMO
- **Anti-adhesive, mimicking the attachment sites for certain pathogens and blocking their adhesion, colonization, and invasion**
- **Reported to alter intestinal epithelial cell to alter expression of pathogen virulence**



HMO's <1% absorbed

Th2 promoting ---- anti-inflammatory

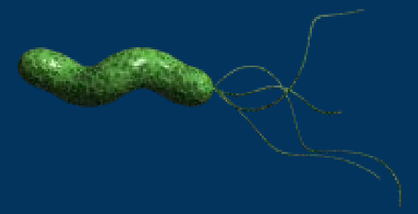
decrease IL-12, IFN

increase IL-10

Gibson GR, et al . Nutr Res Rev . Dec 2004 Yu ZT, et al . Glycobiology. 2013 Chen C, et al.Glycobiology .2013
Bode L. Glycobiology . 2013 Kulinich A et al Carbohydrate Res 2016

Cancer association with inflammation

- Estimated that 20% of cancer death worldwide are related to chronic infection and/or inflammation
  - gastrointestinal and lung cancers accounting for the substantial portion of the total burden
    - Examples: H.pylori, scar carcinoma, UC
    - Human neutrophils can induce malignant transformation which suggests that phagocytic cells are carcinogenic



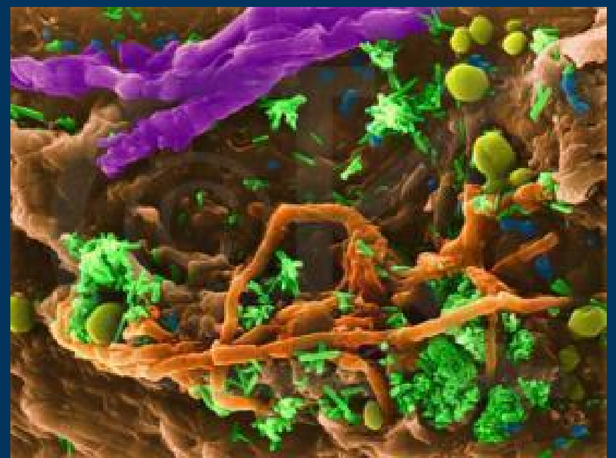
- Inflammation can promote all stages of tumorigenesis

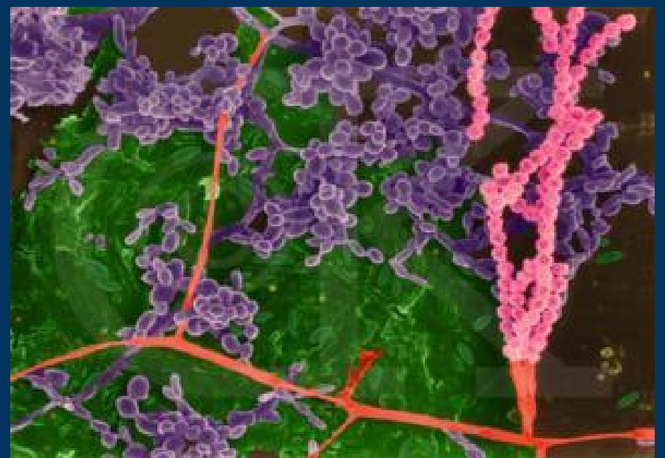
Kamp D Oncology 2011
Morowitz MJ Ann Surg 2011

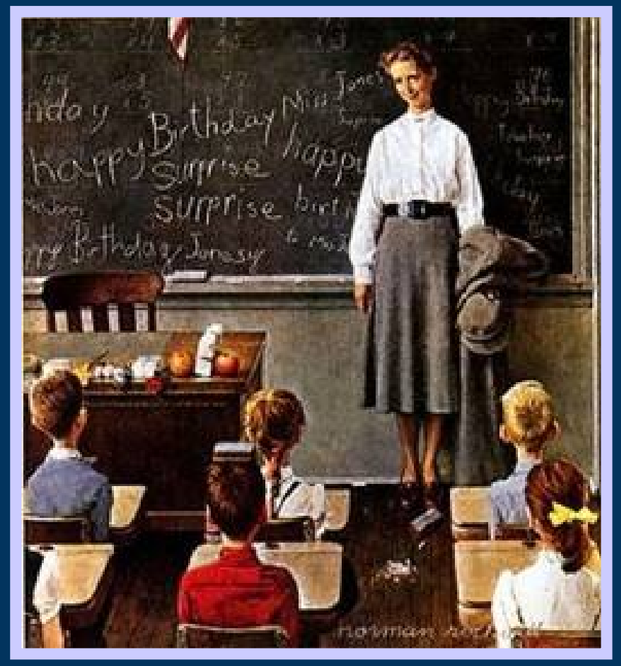
It time for a paradigm shift !

Supply adequate viable beneficial bacteria or a substrate which enhances these specific beneficial bacteria instead of trying to eliminate the pathogen ?

“Bioecological control”







"…, one of the greatest opportunities to improve patient outcomes will probably come not from discovering new treatments but from more effective delivery of existing therapies."

Pronovost PJ et al., Lancet 2004; 363:1061-7