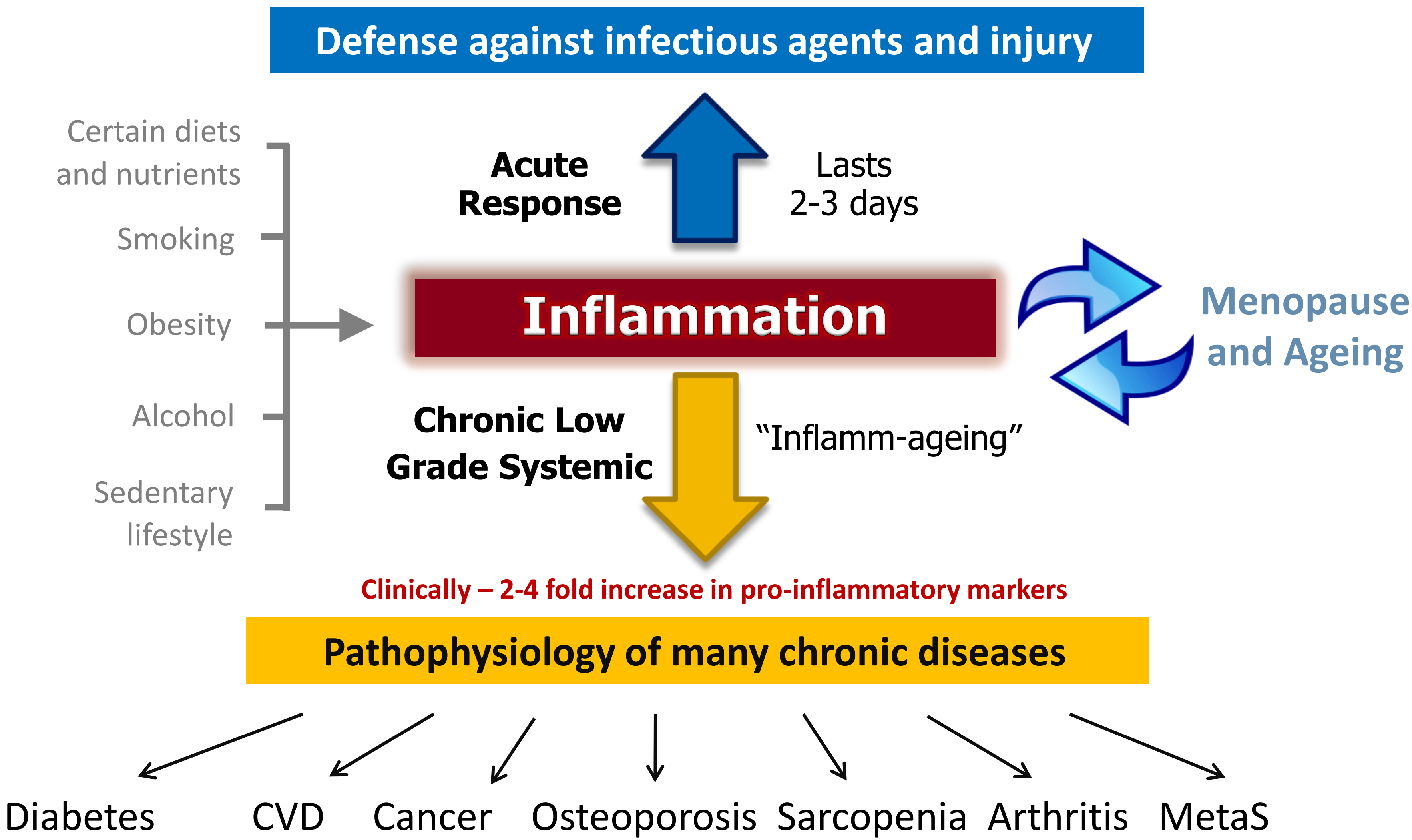
http://www.lga.sa.gov.au/page.aspx?u=283

Short-term Friend, Long-term Foe



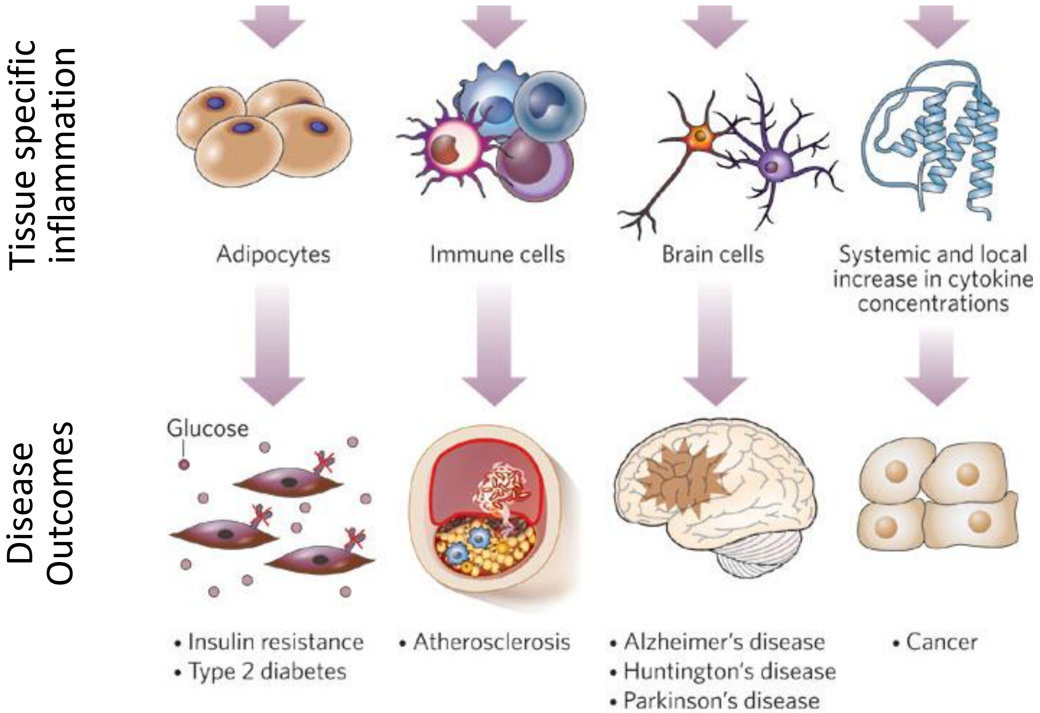
Tissue Specific Inflammation

Inactivity

Obesity

Chronic Systemic Inflammation

Inflammation in certain tissues is linked to the development of many chronic diseases



Handschin & Spiegelman Nature 454, 463-469, 2008

http://content.time.com/time/covers/0,16641,20040223,00.html

Chronic, low grade systemic inflammation often has <u>no</u> symptoms

http://content.time.com/time/covers/0,16641,20040223,00.html

MLA and DAA Symposium: Getting the Right Balance: Novel Approaches for Addressing Dietary Imbalances

Nutrition, Inflammation and Ageing

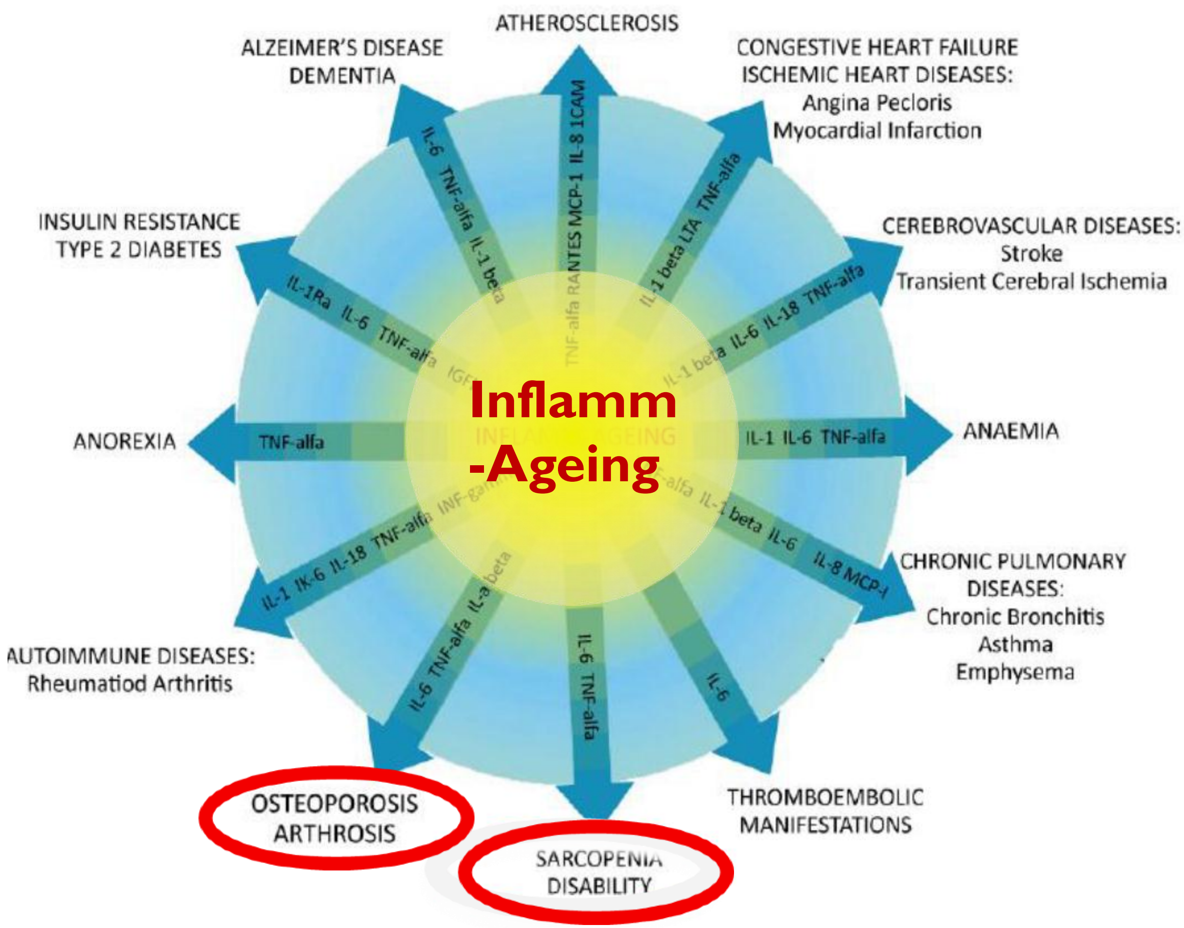
'Inflamm-ageing' and its impact on muscle and bone loss

Robin M. Daly *PhD FASMF*
Professor | Chair of Exercise and Ageing
Centre for Physical Activity and Nutrition Research (C-PAN)
Deakin University, Burwood,
Melbourne, Australia

Email: rmdaly@deakin.edu.au

Inflamm-Ageing

"Inflamm-ageing" is the term used to describe the chronic inflammatory state that is caused by ageing and results in an increase of pro-inflammatory cytokines.

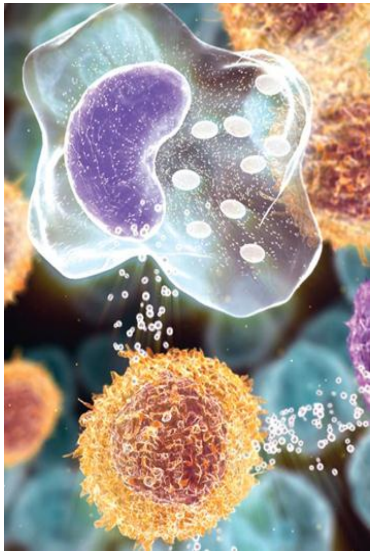


De Martini, Franceschi Monti & Ginaldi, 2006

Pro- and Anti- Inflammatory Markers

Cytokine Imbalance Linked to Common Chronic Diseases

- CRP
- IL-6
- TNF-α
- IL-1
- IL-12
- IL-17
- IL-1α
- Fibrinogen
- IFN-γ



- IL-10
- Adiponectin
- IL-4
- IL-6
- TGF-β
- IL-1Ra

Most cytokines are stimulated or inhibited by other cytokines, thereby creating a network of synergistic cytokine actions

Pro-inflammatory

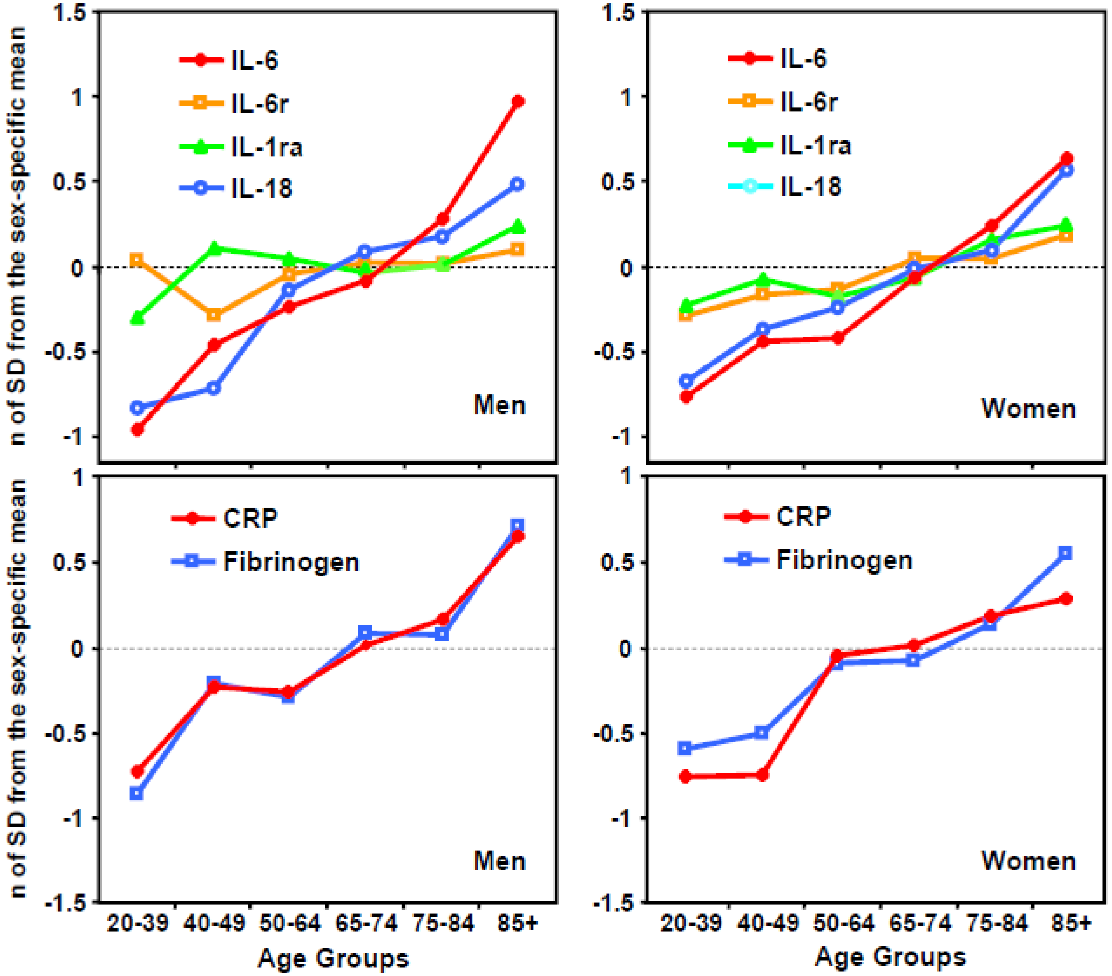
Potentiate bone loss by increasing osteoclast generation and activation or by inducing RANKL expression by osteoblasts

Anti-inflammatory

Inhibitors of osteoclastogenesis by blocking RANKL signalling, either directly or indirectly.

Age-related Pro-inflammatory State

InCHIANTI Study: 595 men and 748 women aged 20-102 years



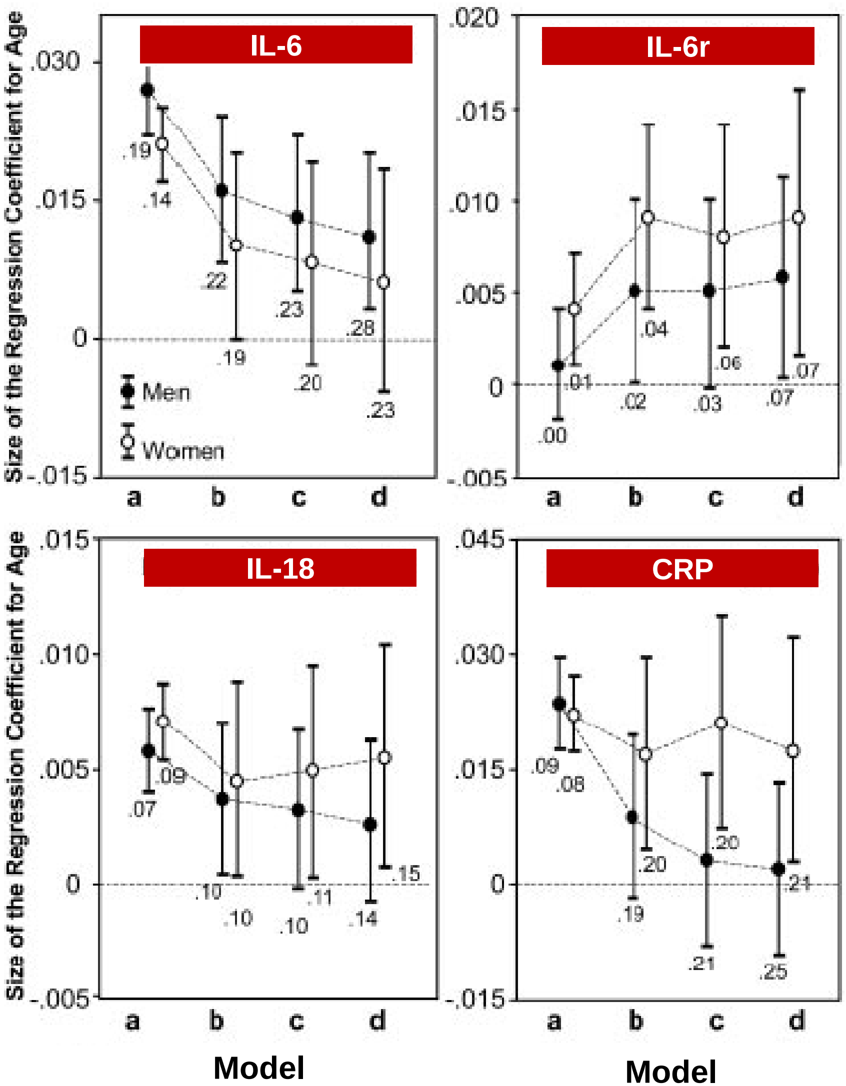
Cytokines

Intercellular signaling proteins that exert pro- and anti-inflammatory activities through the ligation of specific receptors or stimulating the hepatic production of acute phase proteins (eg. CRP and fibrinogen).

Mean values of inflammatory markers according to sex and age group expressed as number of standard deviations from the population mean to make them independent of different units of measure.

Ferrucci L et al. Blood 2005;105:2294-2299

Age-related Pro-inflammatory State



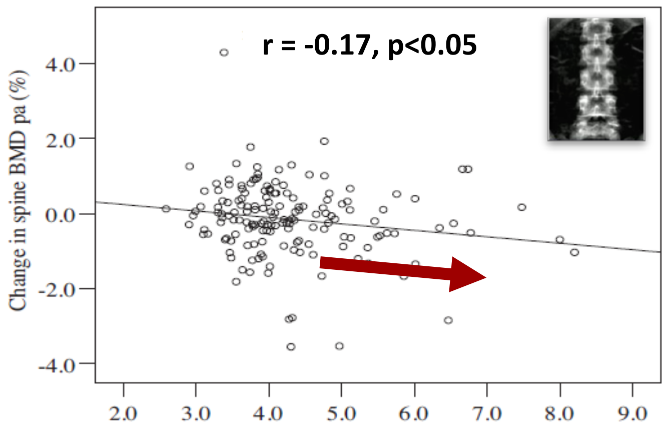
Adjusting for cardiovascular and related risk factors attenuated the age-related increase in some, but not all, inflammatory markers (varied by gender).

Figure 2. Age regression coefficients and their 95% CIs estimated from linear models predicting level of inflammatory markers. Model "a" estimates the crude affect of age; model "b" is adjusted for cardiovascular risk factors; model "c" is also adjusted for subclinical cardiovascular diseases; and model "d" is adjusted for CHD, CHF, stroke, PAD, COPD, diabetes, hypertension, osteoporosis, CFR, cancer, dementia, and depression. R^2 values reported below the confidence interval are for the model used to estimate the age regression coefficients.

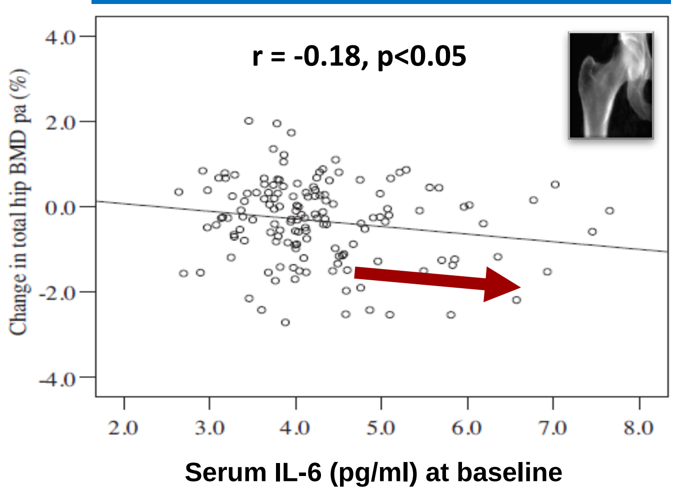
Ferrucci L et al. Blood 2005;105:2294-2299

Inflammation, Bone and Muscle Loss

Change in Spine BMD

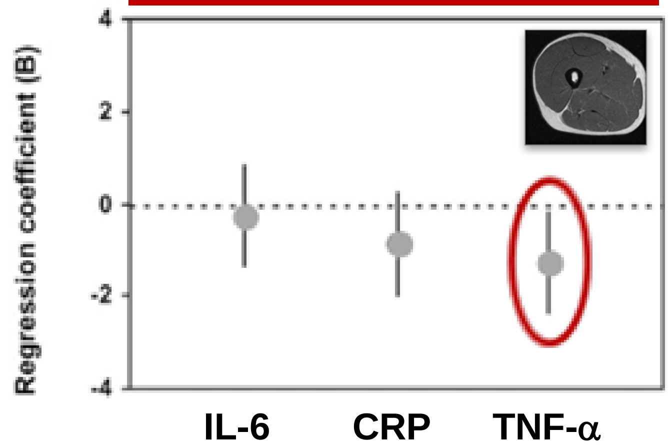


Change in Hip BMD

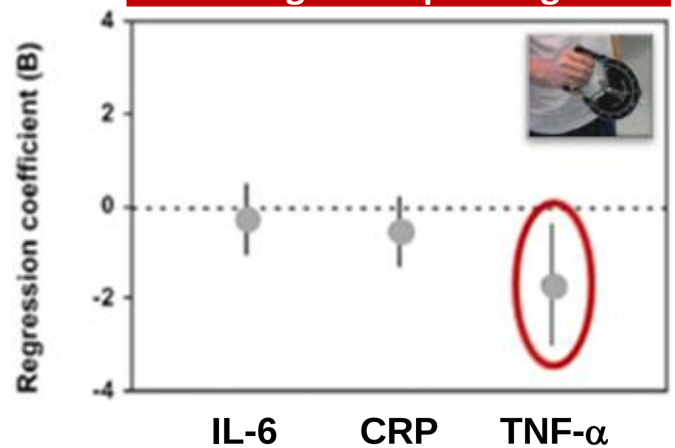


Ding et al. J Clin Endocrinol Metab 93(5): 1952-58, 2008

Change in Muscle Size



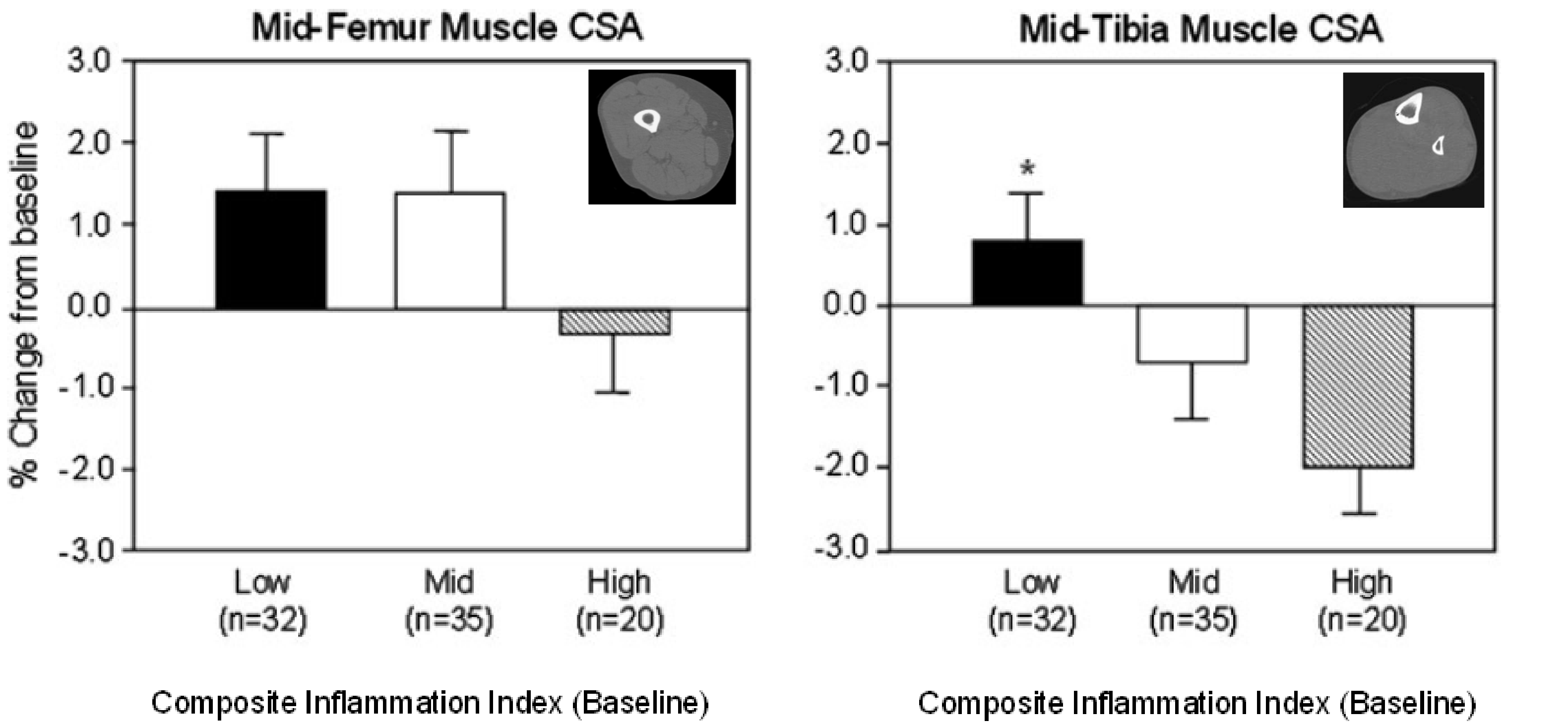
Change in Grip Strength



Schapp et al. J Gerontol A Biol Sci Med Sci 2009: 1-7

Inflammation and Muscle

Low Grade Inflammation Attenuates Exercise induced Muscle Gains



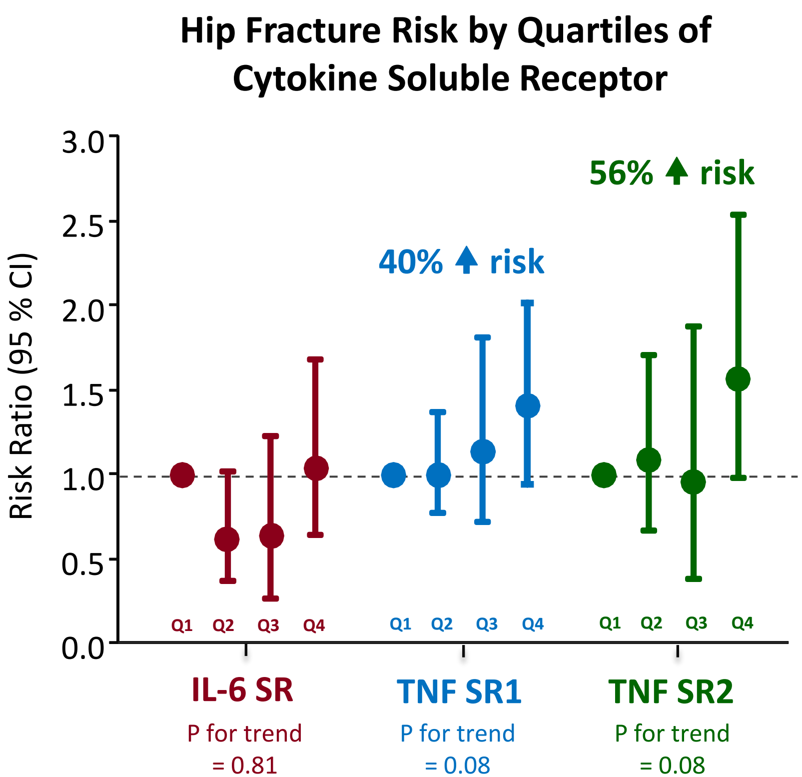
High = two of more inflammatory markers in the highest tertile at baseline, Mid = one marker in the highest tertile at baseline, Low = no marker in the highest tertile at baseline.

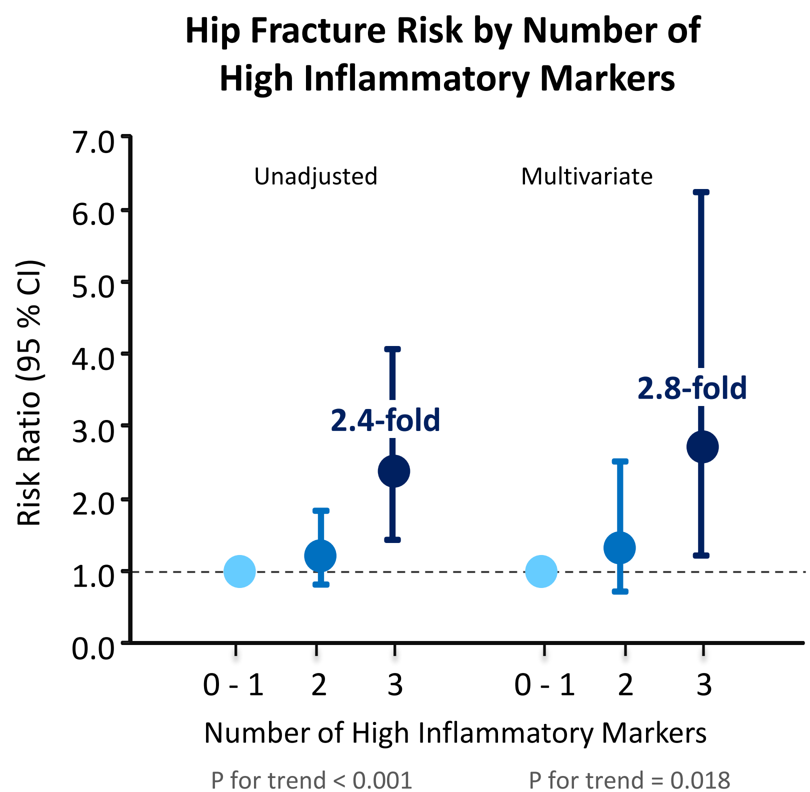
Inflammatory markers that were measured: hsCRP, TNFα and IL-6

Peake et al. Eur J Appl Physiol 2011; 111:3079–3088

Inflammation and Fracture Risk

Nested Case-Control Design; Median 7.1 years Follow-up





400 incident hip fractures and 400 age, race and date of blood drawn matched controls

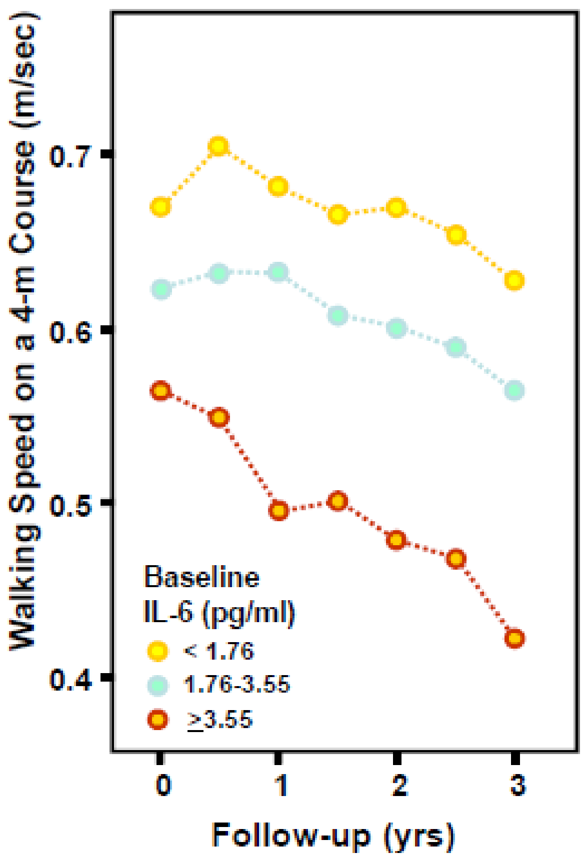
Results independent of BMI, self reported health, physical activity, parental history of fx, diabetes, RA, calcium and vitamin D intake, NSAID, corticosteroid use, frailty, physical function, falls, sex hormones, cystatin-C, BTMs and 25OHD levels

Barbour et al. J Bone Miner Res 27(5):1167-76, 2012

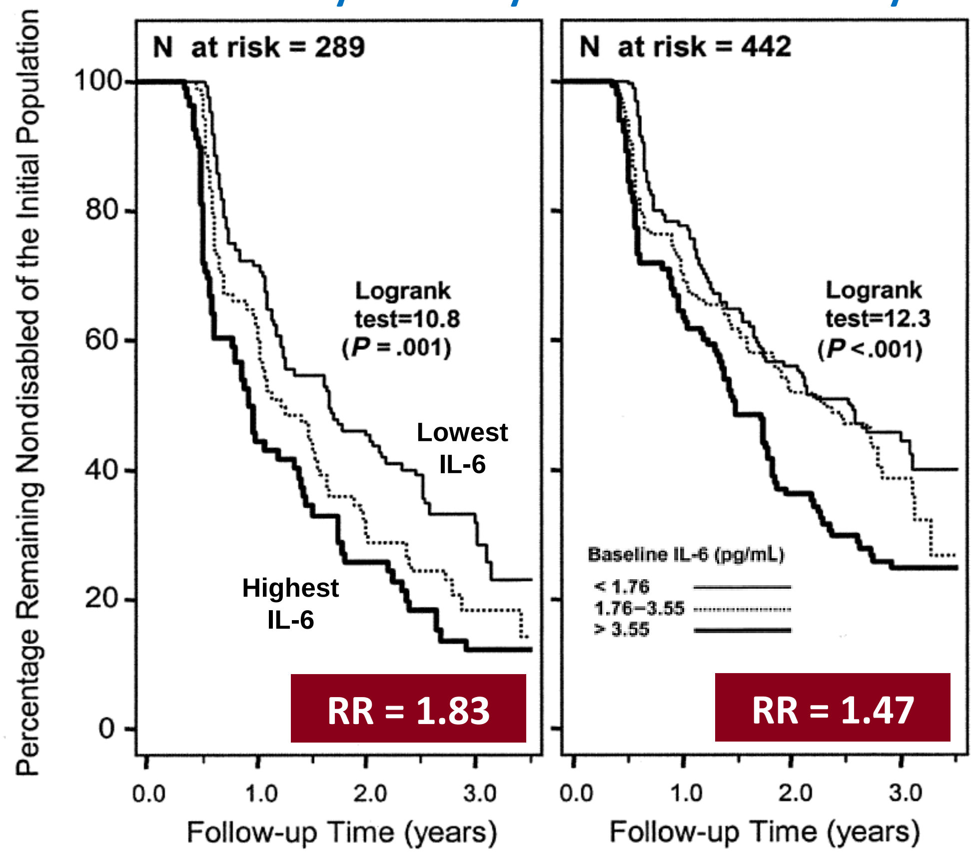
Inflammation and Disability

Women's Health and Ageing Study (n=620 women aged 65+ years)

Walking Speed

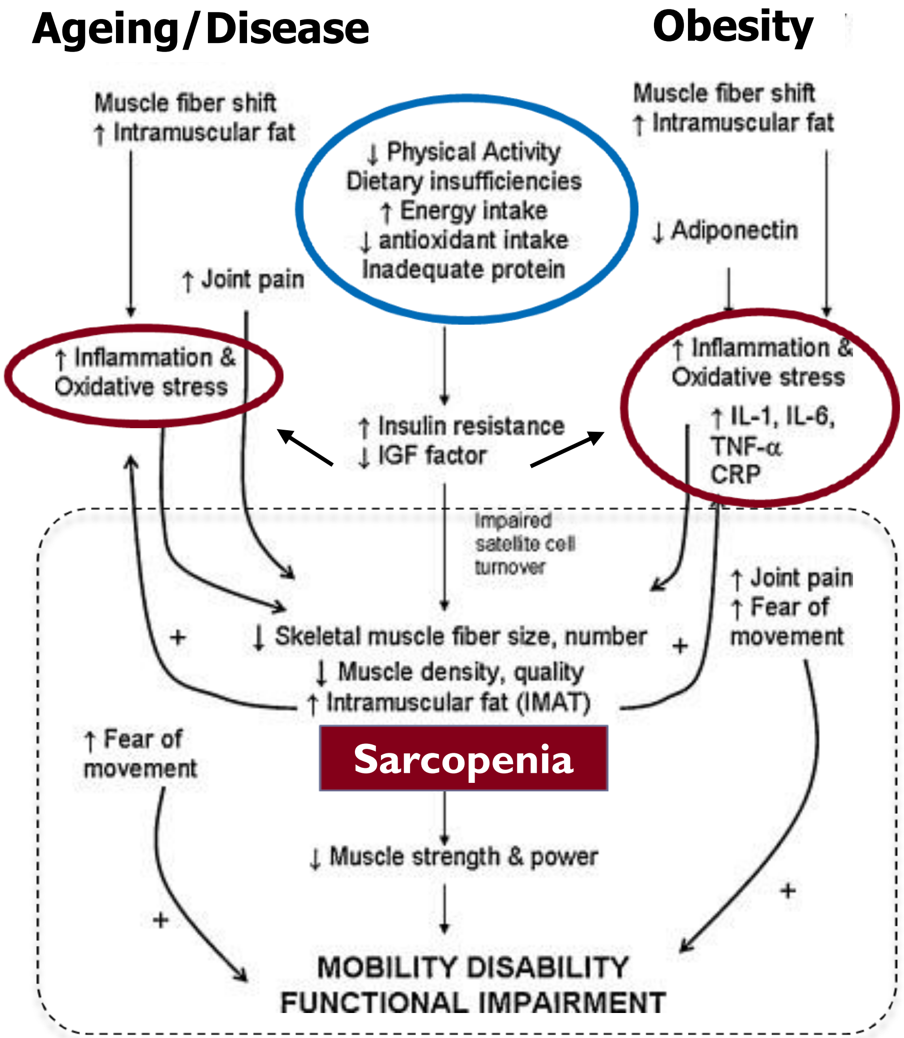


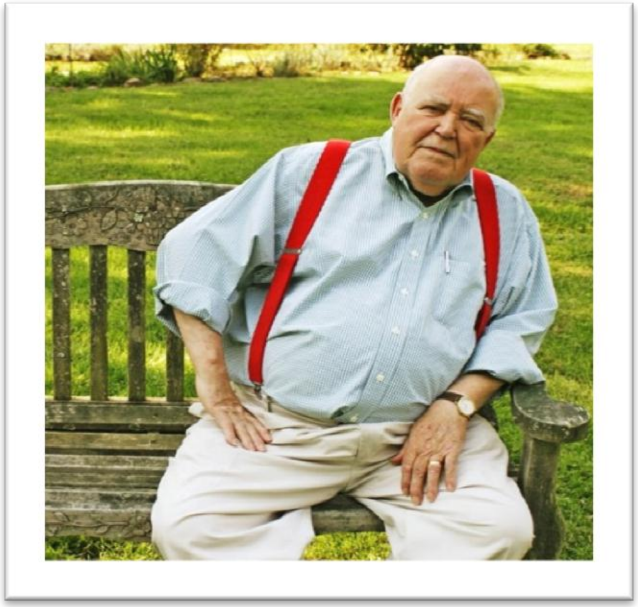
Mobility Disability ADL Disability

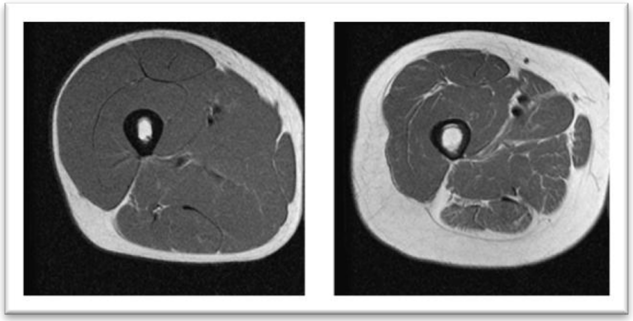


Ferrucci et al. J Geront Med Sci 2002;50:1947-54

Does Fat Modulate the Relationship?



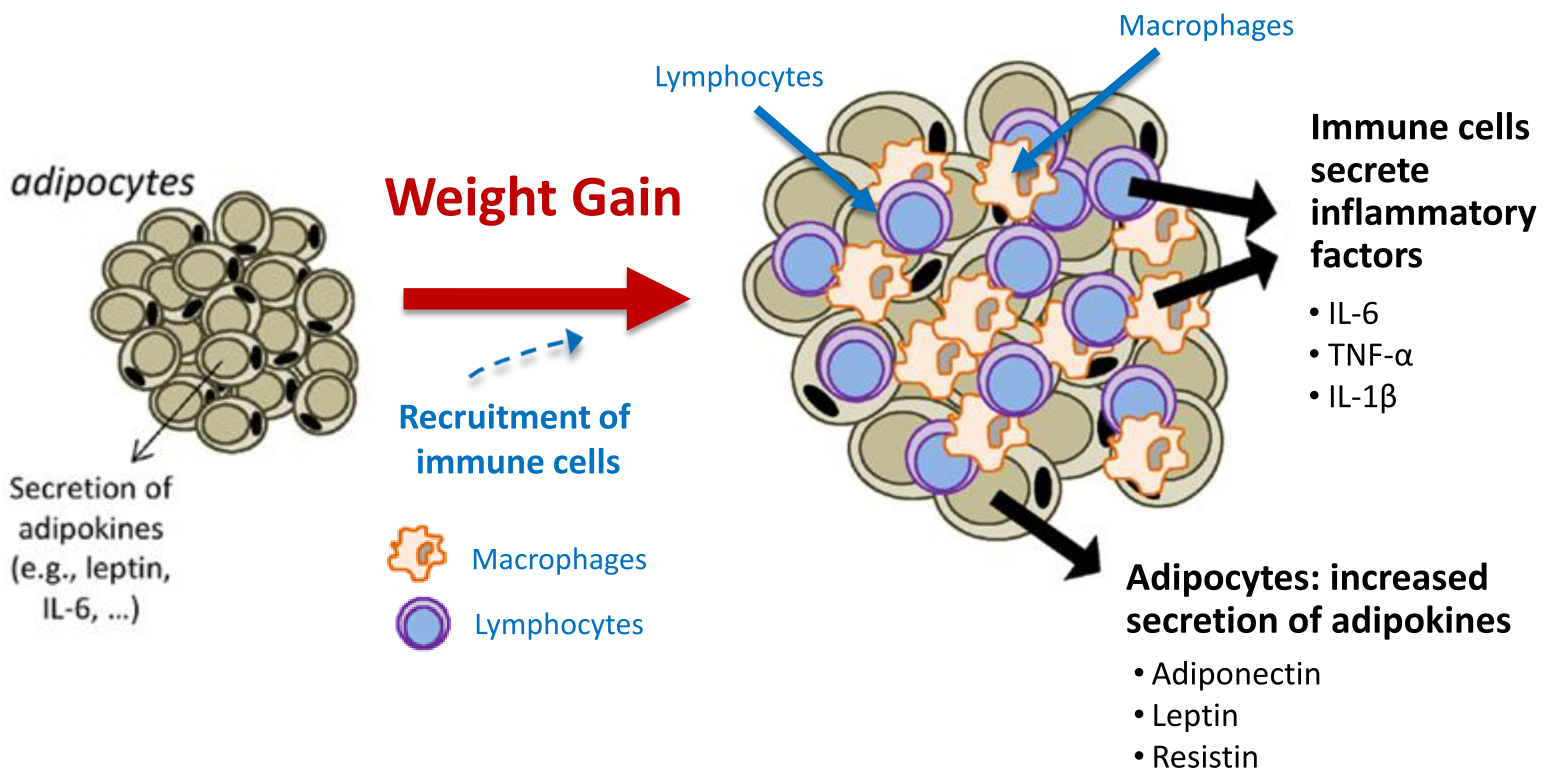




Vincent et al. Ageing Research Review, 2012

Meta-Inflammation

Low-grade, chronic inflammation orchestrated by metabolic cells in response to excess nutrients and energy



Adapted from Castanon et al. Front Endocrinol 15 May 2014

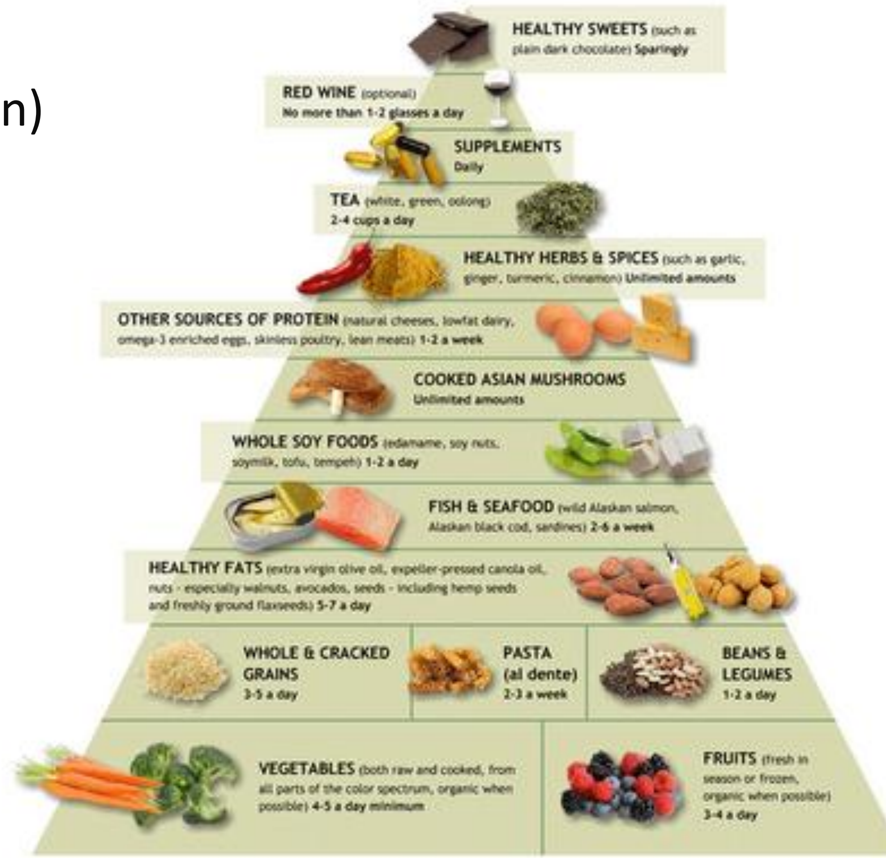
Strategies to Prevent Inflammation

Modifiable Factors Which May Reduce Inflammation

- Exercise
- Weight loss
- Caloric restriction (not malnutrition)
- Certain diets / dietary patterns

Bone and /or muscle

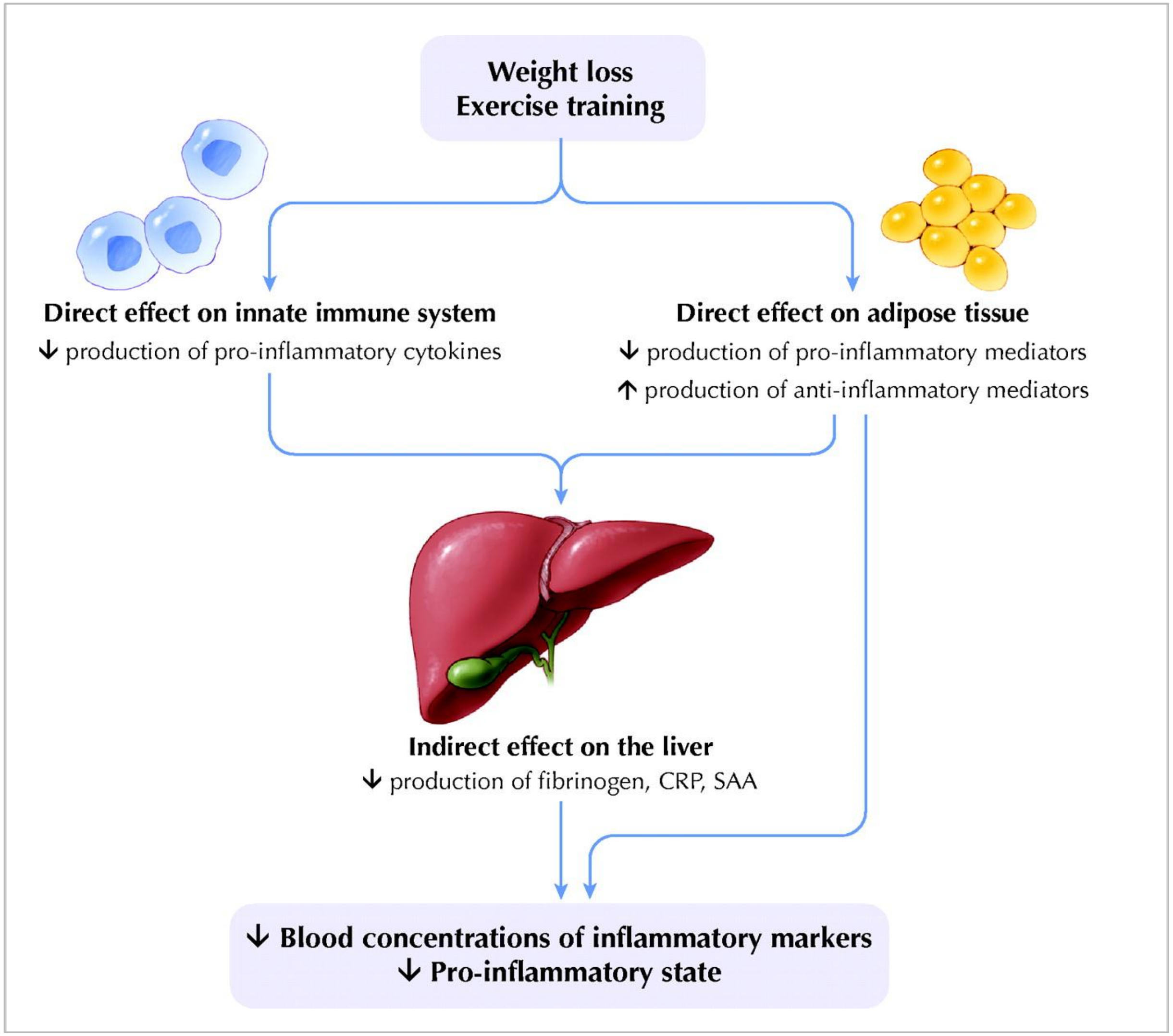
- Calcium / Dairy
- Vitamin D
- Protein / Soy
- Zinc and magnesium
- Vitamin K
- Omega-3 fatty acids
- Fruit and vegetables
- Polyphenols (antioxidants)



http://www.drweil.com/drw/ecs/pyramid/press-foodpyramid.html

Weight Loss, Exercise and Inflammation

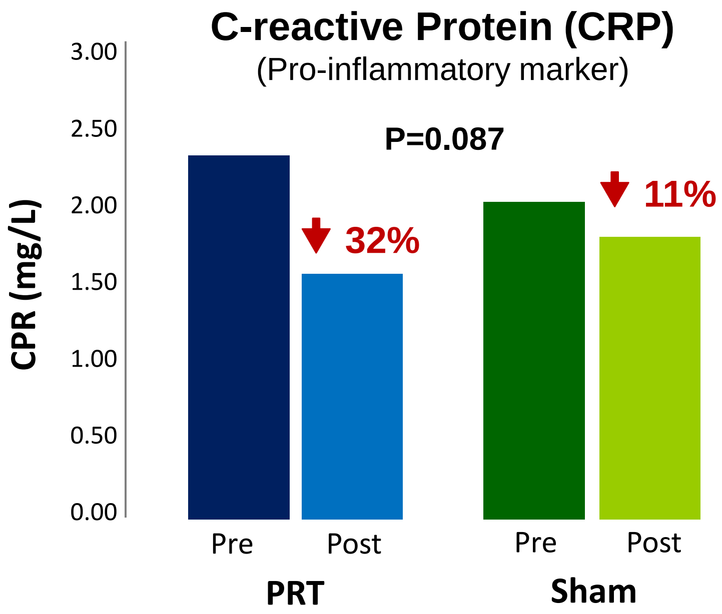
Possible mechanism(s) by which they reduce inflammation

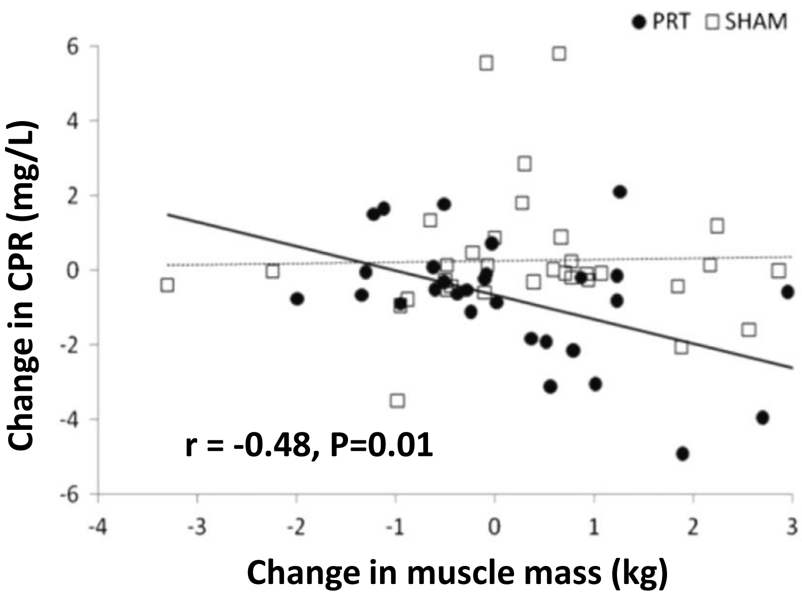


Nicklas et al. CMAJ 272(9): 1199-1209, 2005

Exercise, Muscle and Inflammation

Effects of Progressive Resistance Training on Systemic Inflammation in Older Adults with Type 2 diabetes





Reductions in CRP were mediated, in part, by increases in skeletal muscle (as well as a reduction in fat) following high intensity resistance training

Mavros et al. J Cachexia Sarcopenia Muscle 2014

Strategies to Prevent Inflammation

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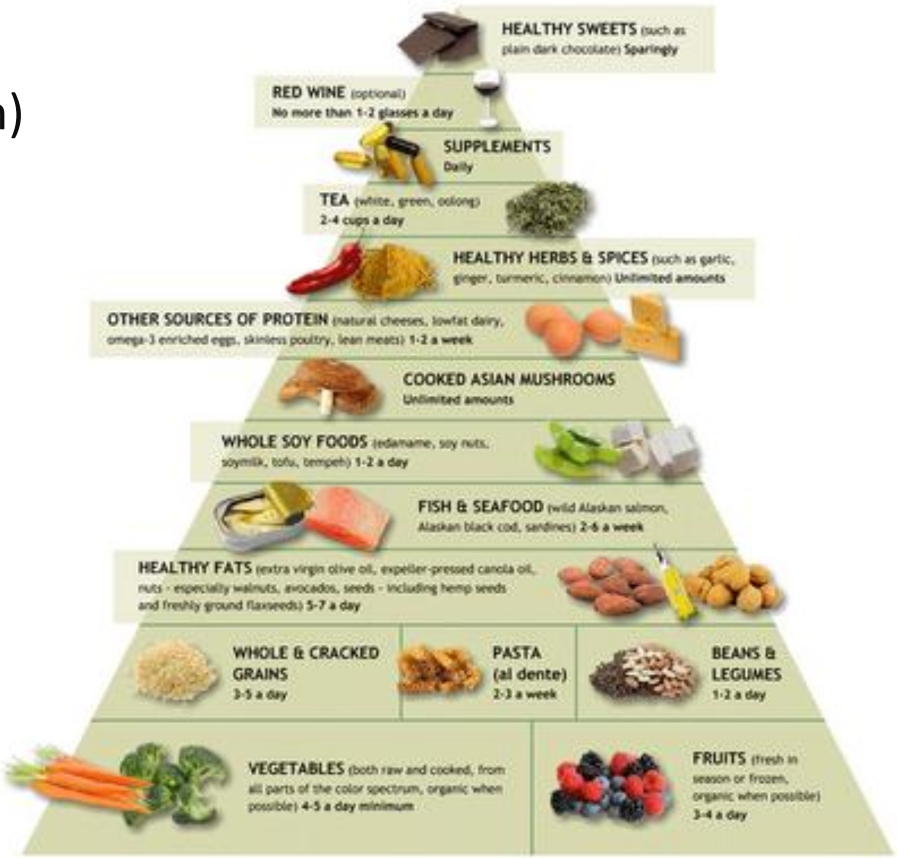
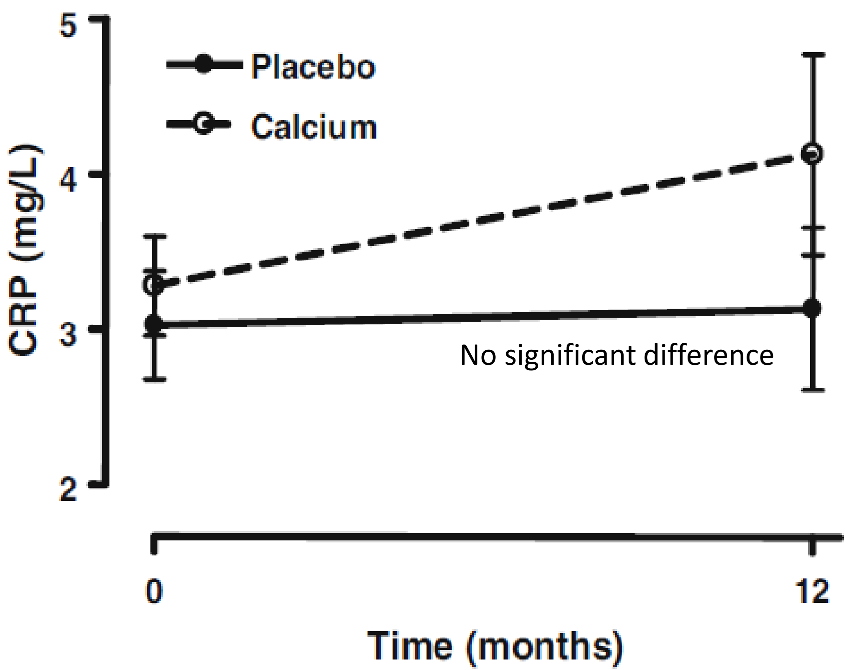


http://www.drweil.com/drw/ecs/pyramid/press-foodpyramid.html

Can Calcium Reduce Inflammation?

12-month RCT: Calcium Citrate (1 g/d)

Healthy postmenopausal women
(calcium citrate n=59; placebo n=57)

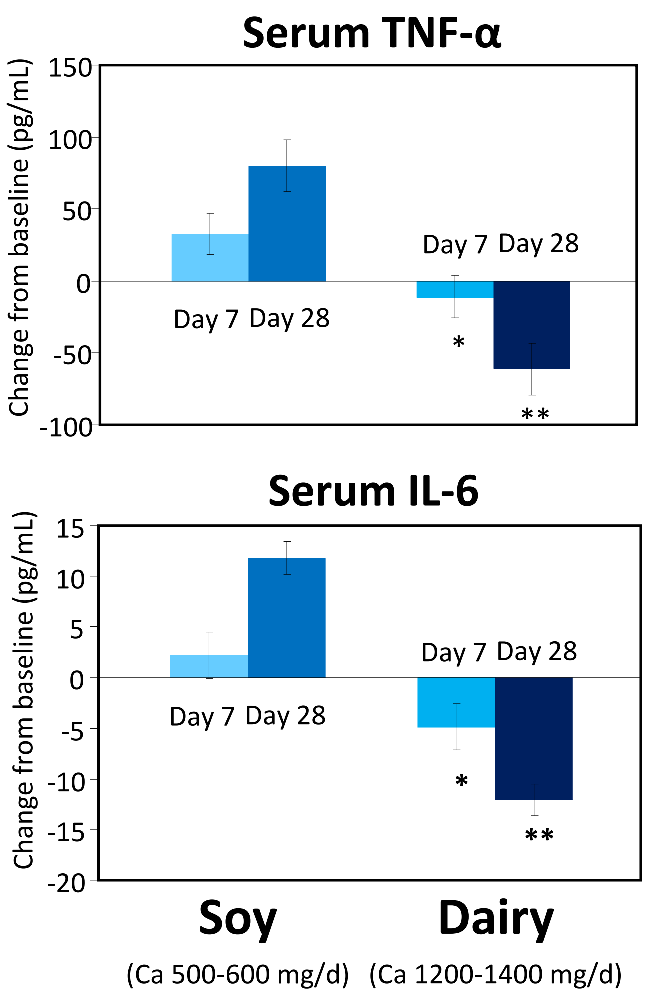


- **Parathyroid hormone (PTH)** stimulates IL-6 and TNF-α, which in turn increases the production of CRP.
- **Calcium supplementation**, through it effects on suppressing PTH, may therefore decrease inflammation.

- **No effect** of calcium citrate (1g/d for 12 months) on CRP levels in older women.

Grey et al. Osteoporosis Int 2006;17:1141-45

Dairy Intake and Inflammation



Zemel et al. Am J Clin Nutr 2010;91:16–22.

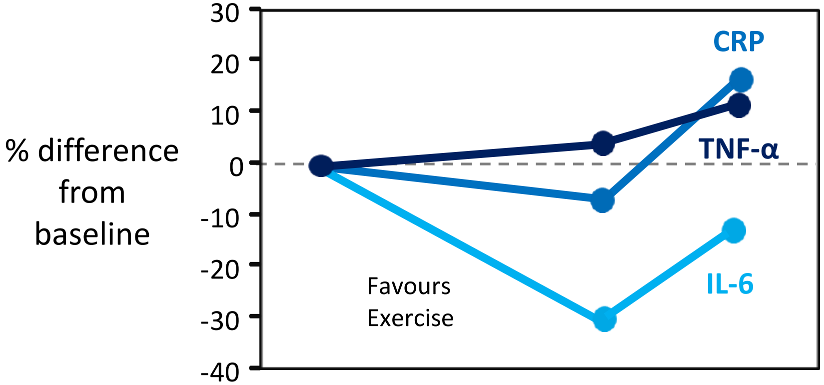
- Some concern that a **high dairy diet** may *increase* inflammation due to an increase in saturated fat and cholesterol.
- A high dairy diet has been associated with a *decrease* in inflammatory markers in **overweight and obese** adults, those with **metabolic syndrome** and **type 2 diabetes**.
- Increased dairy can lead to **improvements** in **body composition** ➔ *confound results*.
- Mixed results on the benefits of **soy protein** on markers of inflammation.

Stancliffe et al. Am J Clin Nutr 2011; Zemel and Sun. J Nutr 2008; Zemel et al. Am J Clin Nutr 2010; Neyestani et al. J Clin Endocrinol Metab 2012 (in press); Josse et al. J Clin Endocrinol Metab 97:251-60, 2012

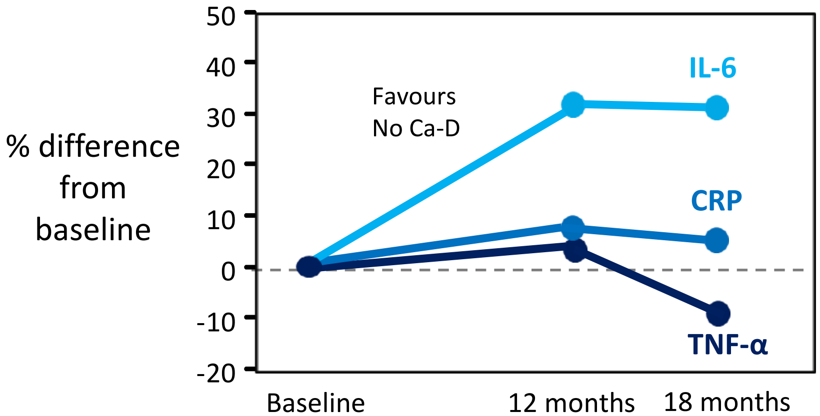
Exercise + Calcium-Vitamin D Fortified Milk

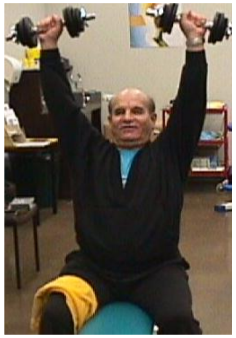
18-month Factorial Design RCT in Healthy Men Aged 50-79 years

Exercise vs No-exercise



Calcium-Vitamin D vs No Ca-D





High intensity PRT (60-80% 1 RM) plus WB impact exercise, 3/week

2 x 200 ml tetra packs per day (1000 mg calcium; 800 IU vitamin D_3; 836 kJ energy, 13.2 g protein, 4.4 g fat)

Peake et al. Eur J Appl Physiol 2011;111(12):3079-88

Dairy Intake and Inflammation

Impact of dairy products on biomarkers of inflammation: a systematic review of randomized controlled nutritional intervention studies in overweight and obese adults[1–3]

Marie-Ève Labonté, Patrick Couture, Caroline Richard, Sophie Desroches, and Benoît Lamarche

ABSTRACT

Background: Recent data from cross-sectional studies suggest that consumption of dairy products is inversely associated with low-grade systemic inflammation, but a cause-and-effect relation can be confirmed only with results from randomized controlled trials.

Objective: We reviewed the results of randomized controlled nutritional intervention studies that have assessed the impact of dairy product consumption (ie, milk, yogurt, and/or cheese) on biomarkers of inflammation in adults (aged ≥18 y).

Design: We performed a systematic literature search in PubMed in April 2012, which was limited to randomized controlled trials in humans published in English. Studies that included pregnant or lactating women or that did not include a low-dairy control intervention were excluded.

Results: Eight trials that were conducted in overweight or obese adults were included in the review. The only study that had identified change in the inflammatory profile as its primary outcome measure showed that dairy food consumption improved pro- and antiinflammatory biomarker concentrations compared with the low-dairy control diet. Three of the 7 studies in which inflammation was a secondary or undefined outcome showed improvement in key inflammatory biomarkers, ie, C-reactive protein, IL-6, or TNF-α after dairy product consumption, whereas the other 4 studies showed no effect.

Conclusions: Dairy product consumption does not exert adverse effects on biomarkers of inflammation in overweight or obese adults. Several methodologic factors and limitations among existing studies do not allow differentiation between a beneficial or neutral impact of dairy products on inflammation. Further studies specifically designed to assess inflammation-related outcomes are warranted. Am J Clin Nutr 2013;97:706–17.

Key Findings

- Dairy product consumption ***does not*** exert adverse effects on biomarkers of inflammation in overweight or obese adults.
- Several methodologic factors and limitations among existing studies do not allow differentiation between a beneficial or neutral impact of dairy products on inflammation.

The American Journal of Clinical Nutrition

Labonte et al Am J Clin Nutr 2013;97:706-17

Strategies to Prevent Inflammation

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- Certain diets / dietary patterns

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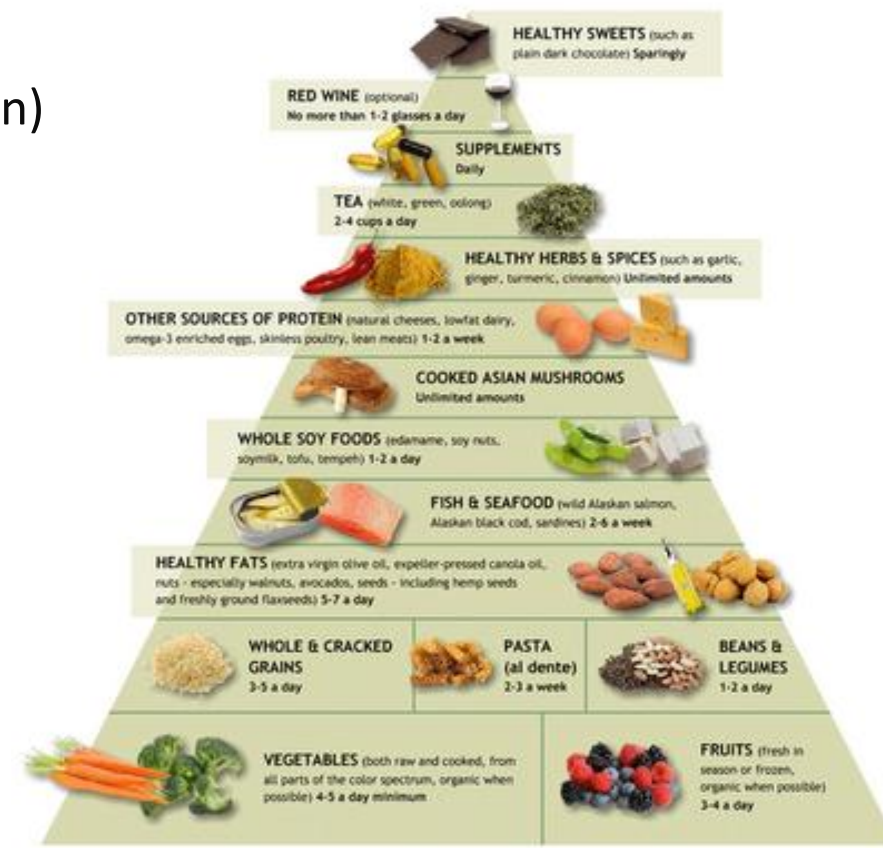
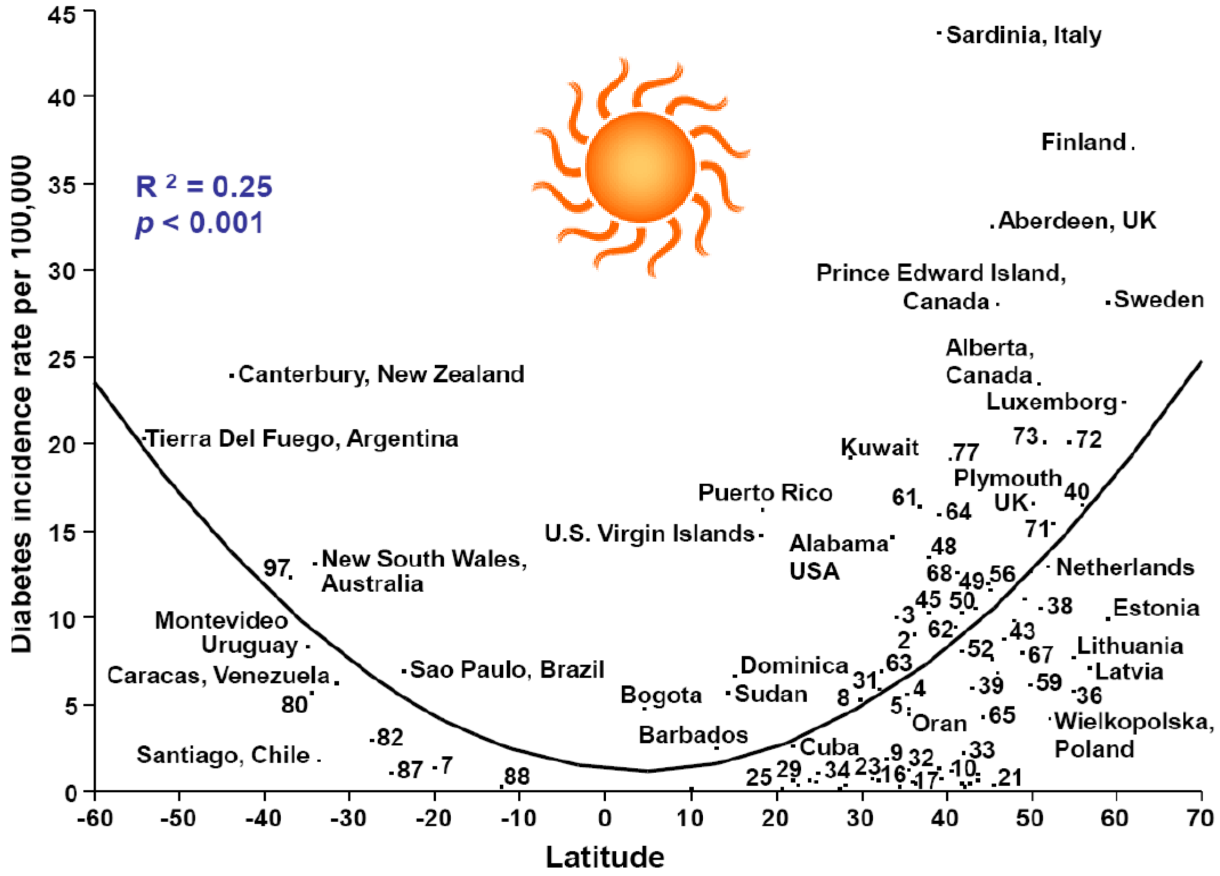
- Zinc and magnesium
- Vitamin K
- Omega-3 fatty acids
- Fruit and vegetables
- Polyphenols (antioxidants)



http://www.drweil.com/drw/ecs/pyramid/press-foodpyramid.html

Vitamin D and Autoimmune Disease

Incidence of Type 1 Diabetes by Latitude



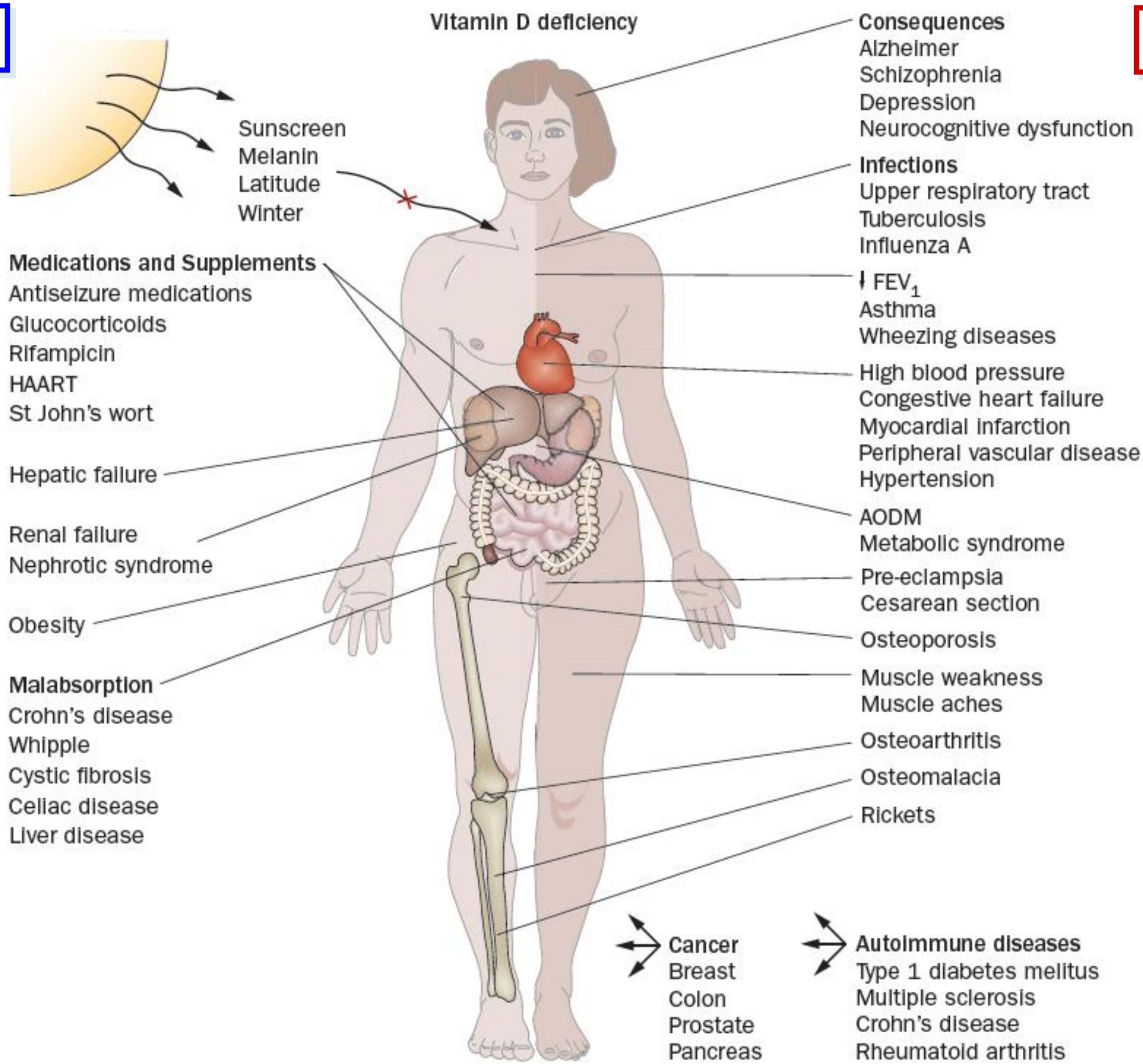
Incidence rates of type I diabetes in 51 regions by latitude; young men, aged 0-18 years, 1990-94

Mohr et al Diabetologia 2008 Aug;51(8):1391-8.

Vitamin D Deficiency
Causes and Consequences

Causes

Consequences

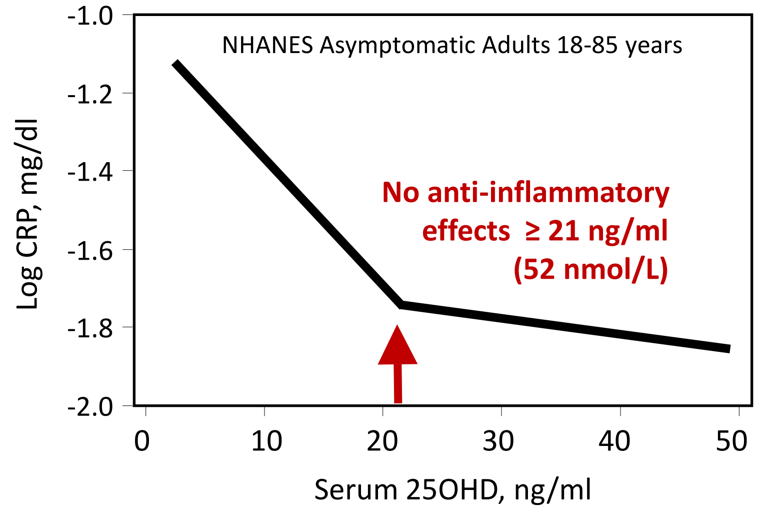


Holick, M. F. *Nat. Rev. Endocrinol.* 7, 73–75 (2011); doi:10.1038/nrendo.2010.234

Can Vitamin D Reduce Inflammation?

- **Mixed findings** from epidemiological and observational studies.
  - *May depend on vitamin D status [25(OH)D] and the health status of the individual.*

  Shea et al. Am. J. Epidemiol 167: 313-320, 2008; Hypponen et al Plos One 5:e10801, 2010; Amer et al. Am J Card 109:226-30, 2012



Amer et al. Am J Card 109:226-30, 2012

- **Vitamin D supplementation** has had a <u>positive</u> effect on cytokine profiles in clinical patients, especially at higher doses (eg. up to 2000 IU/d).
  - *Congestive heart failure, multiple sclerosis, hemodialysis patients, osteoporosis, type 2 diabetes and the critically ill*

Schleithoff et al. Am J Clin Nutr 2006, 83:754-59; Mahon et al. J Neuroimmunol 2003, 134:128-32; Bucharles et al. J Ren Nutr 2011; Shab-Bidar et al. Diab Metab Res Rev 2012; van den Berghe et al. J Clin Endocrinol Metab 2003;88:4623-32.

Is There a Dose Response Effect of Vitamin D?

Incremental doses of vitamin D (200 to 600 IU) for 22 weeks during winter had no effect on cytokine concentrations in young or older adults.

Older Adults	Placebo	5 µg D_3/d (200 IU/d)	10 µg D_3/d (400 IU/d)	15 µg D_3/d (600 IU/d)	*P*
hs-CRP, *mg/L*					
Baseline	2.360 (1.565, 3.468)	2.341 (1.035, 3.969)	2.508 (1.397, 4.886)	2.955 (1.420, 5.070)	
Post-intervention	2.415 (1.197, 4.876)	2.146 (0.972, 3.518)	1.824 (0.937, 3.723)	3.274 (1.286, 5.832)	0.11
IL-6, *ng/L*					
Baseline	1.529 (0.892, 2.616)	1.444 (0.868, 3.075)	1.582 (1.004, 2.458)	1.736 (1.103, 2.700)	
Post-intervention	1.677 (1.134, 2.782)	1.815 (1.033, 2.847)	1.705 (1.068, 3.017)	1.863 (1.368, 3.168)	0.67
IL-10, *ng/L*					
Baseline	0.910 (0.768, 1.182)	1.006 (0.823, 1.190)	0.926 (0.770, 1.147)	0.980 (0.821, 1.167)	
Post-intervention	0.931 (0.807, 1.186)	0.883 (0.787, 1.045)	0.912 (0.743, 1.115)	0.937 (0.804, 1.142)	0.33
sCD40L, *ng/L*					
Baseline	1430 (461, 2926)	1306 (620, 4116)	1376 (445, 2924)	1774 (690, 3388)	
Post-intervention	1505 (218, 3016)	1839 (664, 3574)	1261 (247, 3666)	1643 (486, 3360)	0.51
TGFβ, *ng/L*					
Baseline	7968 (4500, 12547)	8304 (5471, 12011)	8142 (4571, 10606)	8603 (5723, 12452)	
Post-intervention	8181 (4098, 14767)	8691 (4714, 13573)	7076 (2940, 10969)	8775 (4612, 12578)	0.53
TNFα, *ng/L*					
Baseline	1.766 (1.358, 2.224)	1.654 (1.350, 2.109)	1.638 (1.322, 2.316)	1.578 (1.315, 2.055)	
Post-intervention	1.722 (1.332, 2.244)	1.577 (1.311, 2.109)	1.690 (1.267, 1.995)	1.612 (1.317, 1.978)	0.59
Fibrinogen, *g/L*					
Baseline	1.858 (1.247, 2.907)	2.118 (1.444, 3.542)	1.779 (1.248, 2.848)	2.223 (1.312, 3.082)	
Post-intervention	2.189 (1.599, 3.069)	2.099 (1.468, 3.786)	2.017 (1.396, 2.809)	2.183 (1.739, 3.199)	0.89

Young adults (n=211) aged 20-40 years; Older adults (n=202) aged ≥64 years

Barnes et al. J Nutr 2011, 141:476-81

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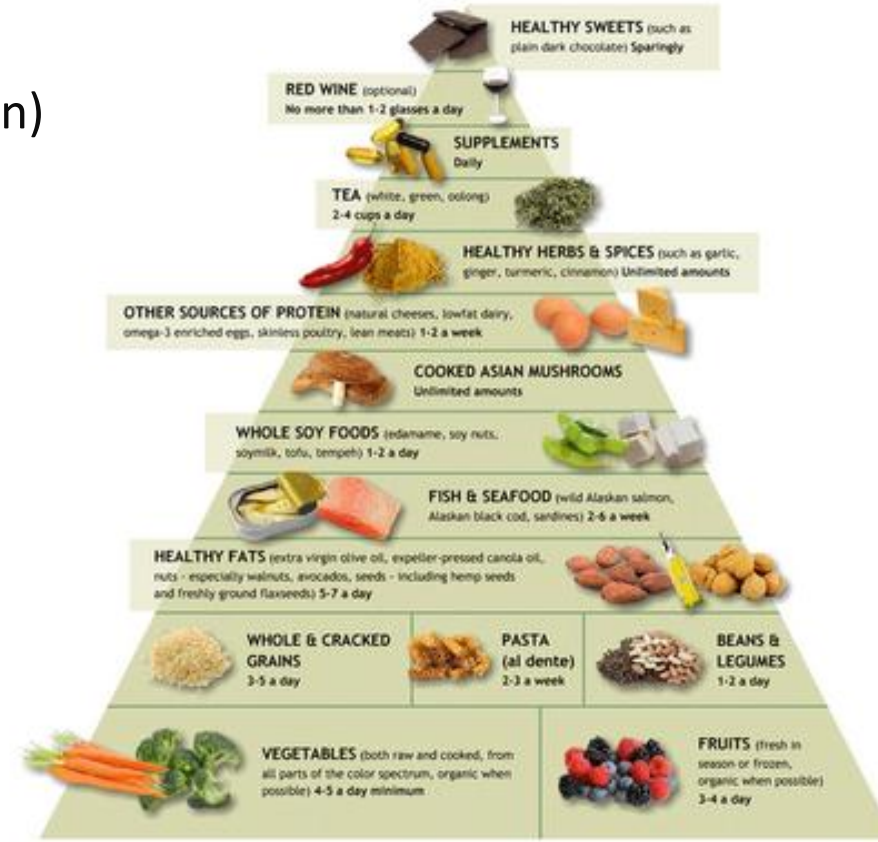
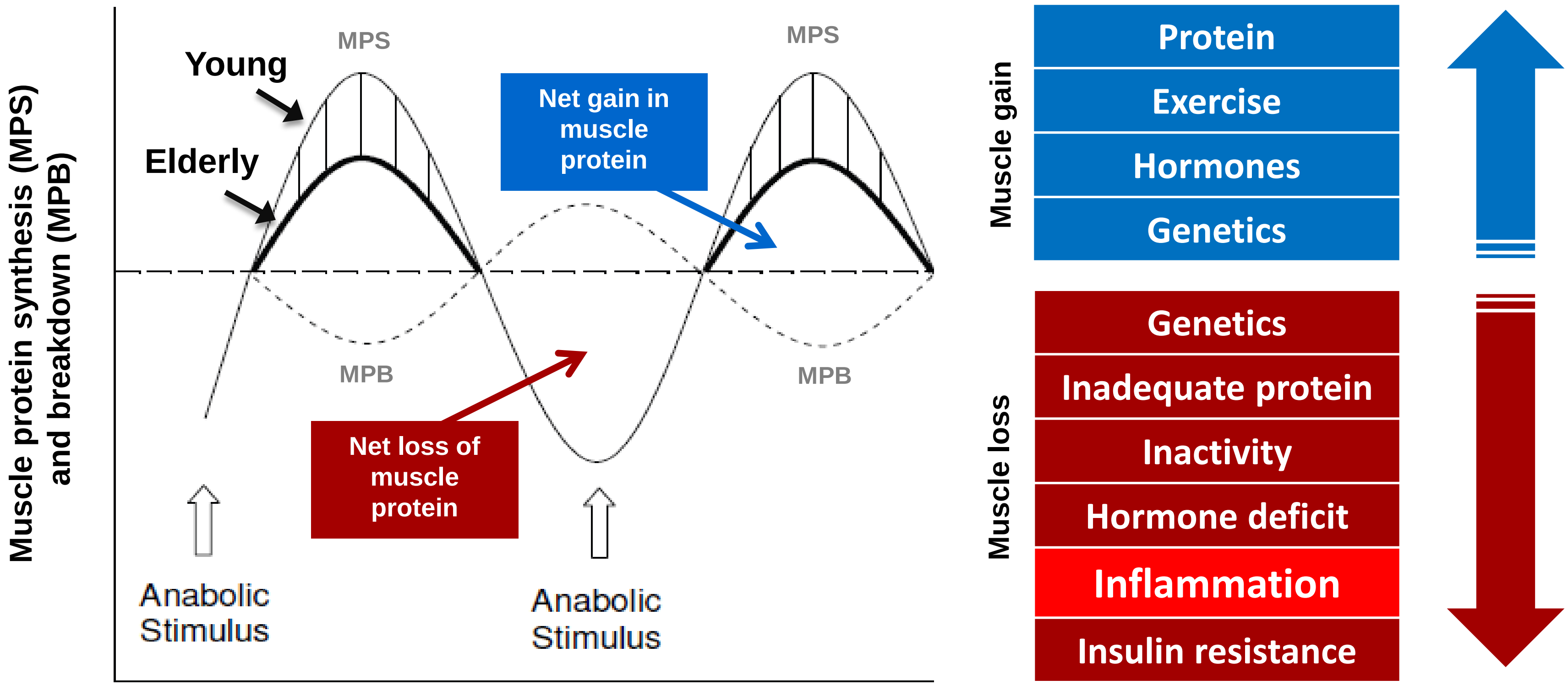


http://www.drweil.com/drw/ecs/pyramid/press-foodpyramid.html

Regulation of Muscle Mass

Balance between Muscle Protein Synthesis and Breakdown

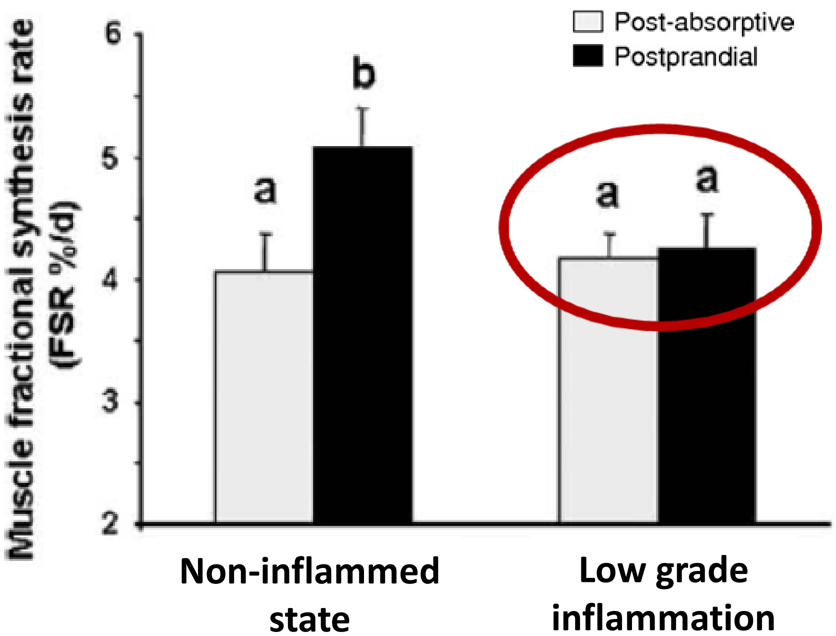


Breen and Phillips. Nutrition and Metabolism 2011:8:68

Regulation of Muscle Mass

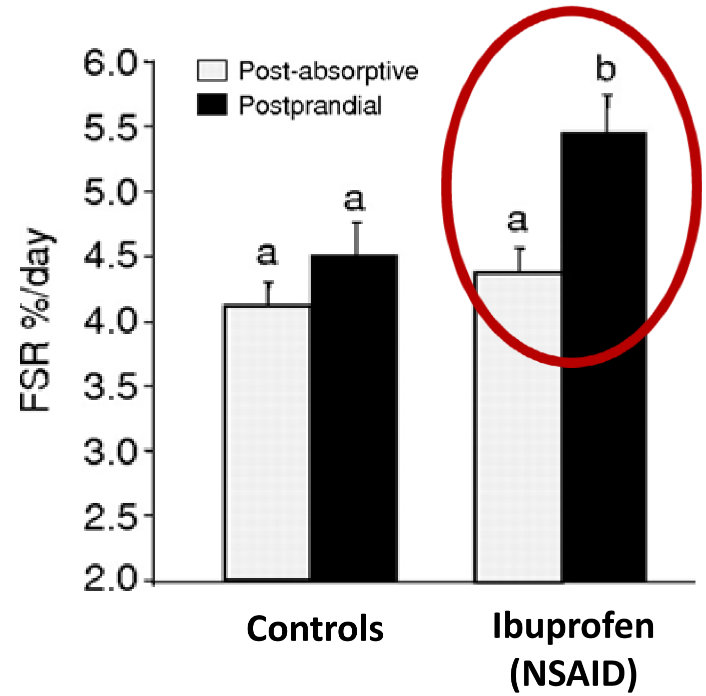
Effects of Inflammation on Muscle Protein Synthesis (MPS)

Low grade inflammation impairs the MPS response to feeding in rats.



Balage et al. J Nutr Biochem. 2010 Apr;21(4):325-31

Prevention of inflammation maintained the anabolic response to feeding in rats.

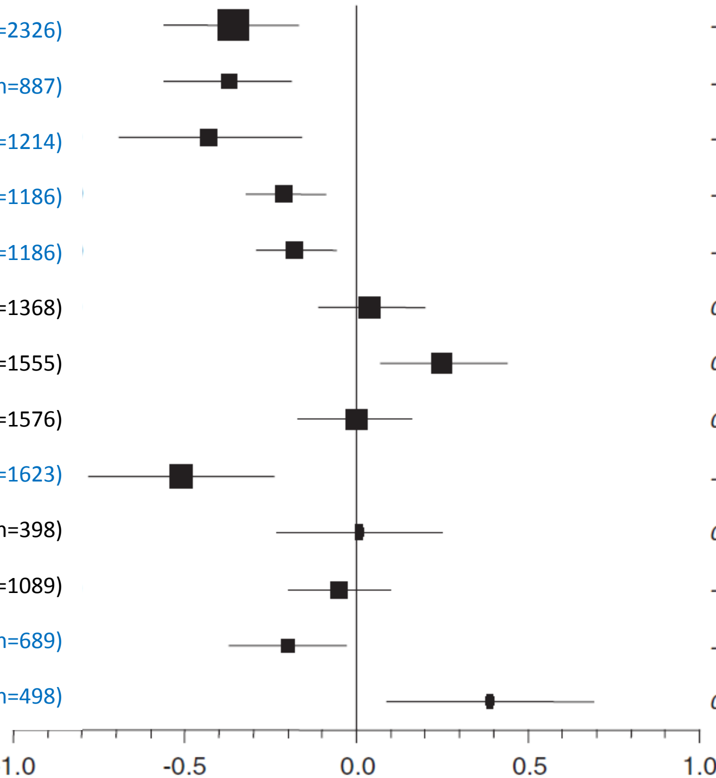


Rieu I et al. J Physiol 2009;587:5483-5492

Health Benefits of High Protein Diets

A systematic review and meta-analysis of RCTs in healthy adults

Health outcomes	Standardised Mean Difference (95% CI)
Weight loss (n=2326)	-0.36 (-0.56, -0.17)
BMI (n=887)	-0.37 (-0.56, -0.19)
Waist circumference (n=1214)	-0.43 (-0.69, -0.16)
Systolic BP (n=1186)	-0.21 (-0.32, -0.09)
Diastolic BP (n=1186)	-0.18 (-0.29, -0.06)
Total cholesterol (n=1368)	0.04 (-0.11, 0.20)
HDL-c (n=1555)	0.25 (0.07, 0.44)
LDL-c (n=1576)	0.00 (-0.17, 0.16)
Triglycerides (n=1623)	-0.51 (-0.78, -0.24)
C-reactive protein (n=398)	0.01 (-0.23, 0.25)
Fasting glucose (n=1089)	-0.05 (-0.20, 0.10)
Fasting insulin (n=689)	-0.20 (-0.37, -0.03)
Satiety (n=498)	0.39 (0.09, 0.69)



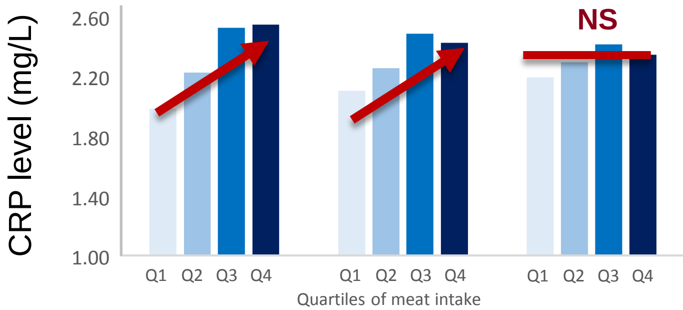
SMDs (difference between change values from baseline).

Santesso et al. Eur J Clin Nutr (2012) 66, 780–788

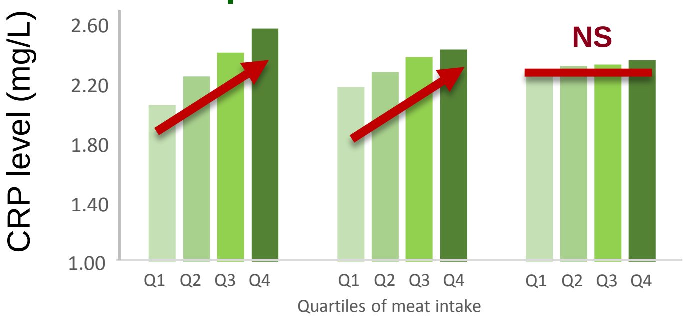
Red Meat Intake and Inflammation

Cross-sectional Nurses' Health Study: 3690 women diabetes free

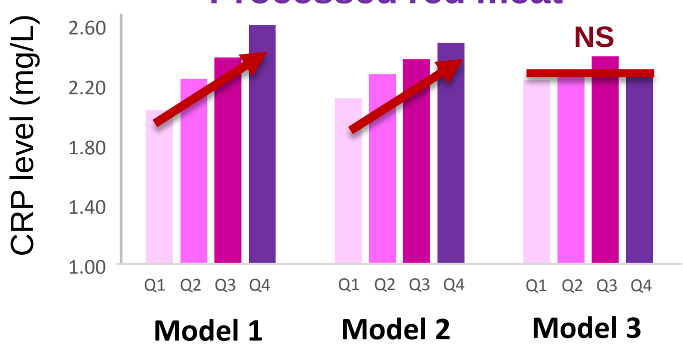
Total Red Meat Intake



Unprocessed red meat



Processed red meat



Greater meat intake was associated with an increased in the pro-inflammatory marker CRP, but not after adjusting for BMI.

Model 1: adjusted for age at blood draw, ethnicity and fasting status.

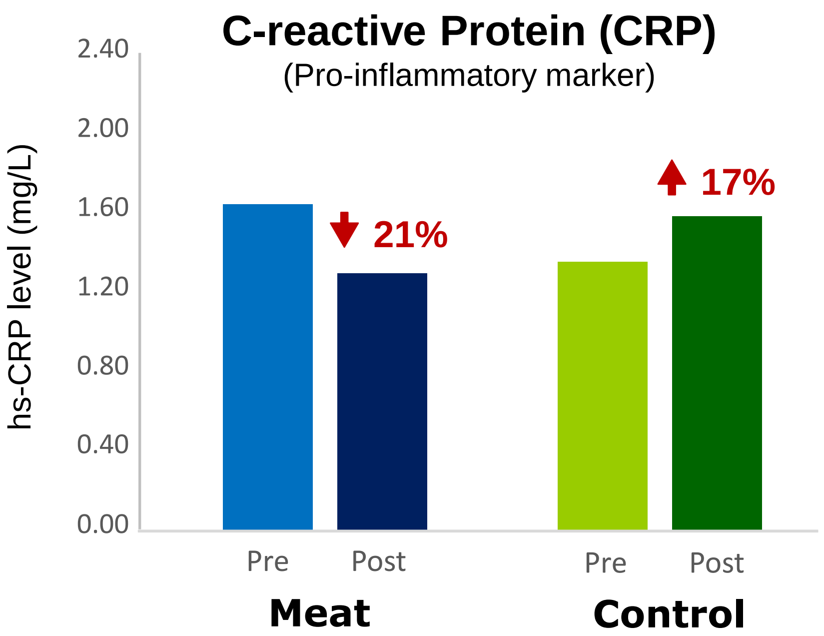
Model 2: adjusted for model 1 + HRT use, family history of diabetes, history of hypertension and hypercholesterolemia, smoking, physical activity, healthy eating index, and total energy intake.

Model 3: adjusted for model 1 and 2 plus BMI

Ley et al. Am J Clin Nutr 2014

Red Meat Intake and Inflammation

Randomised controlled trial (8 weeks) in 60 participants aged >20 years



Meat group: Partially replace energy from carbohydrate-rich foods with protein from lean red meat.

Participants were supplied with *~215 g/d raw weight of lean red meat.* The goal was to achieve 35-40 g/d higher protein intake compared to the control group.

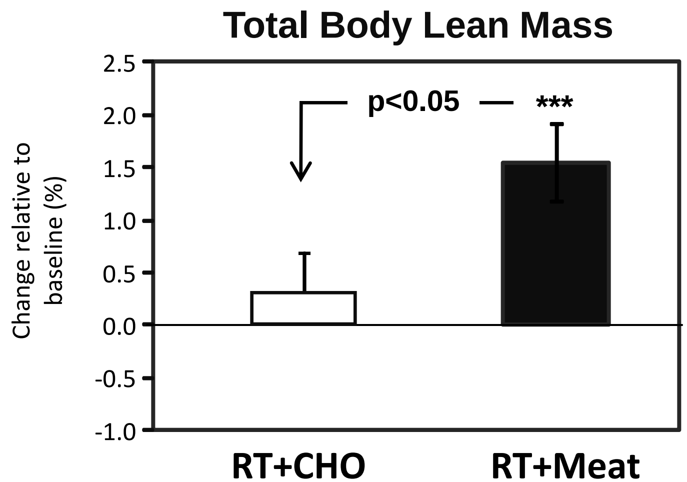
Control group: usual diet

"Our results suggest that partial replacement of dietary carbohydrate with protein from lean red meat does not elevate oxidative stress or inflammation".

Hodgson et al. J Nutr 137:363-67, 2007

Resistance Exercise + Lean Red Meat

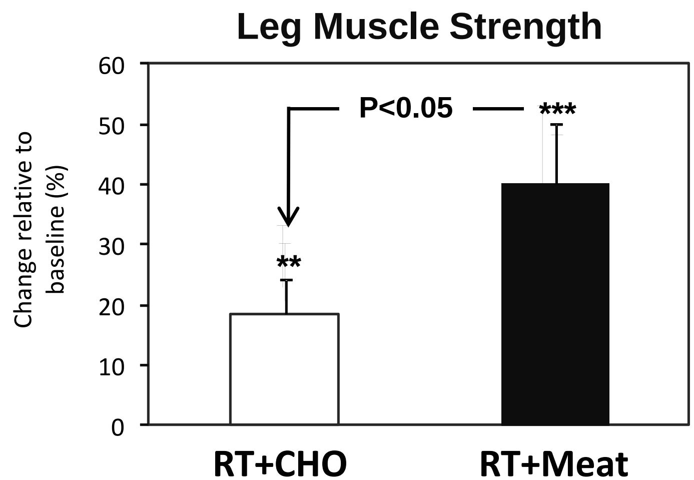
≈160 g cooked lean red meat
(80 g per serve) for 6 d/wk



Total body Lean Mass
- Lean red meat +0.6 kg
- Carbohydrate +0.1 kg

*** $p<0.001$ vs baseline

Wheels on weight van
PRT, 2/week for 14 weeks
3 sets of 8-12 reps



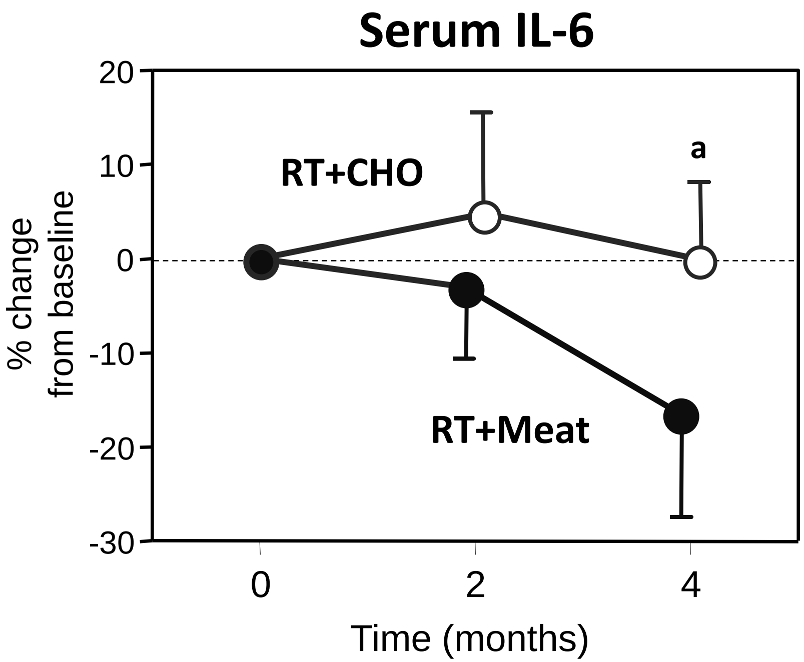
Leg extension strength
- Lean red meat 40%
- Carbohydrate 19%

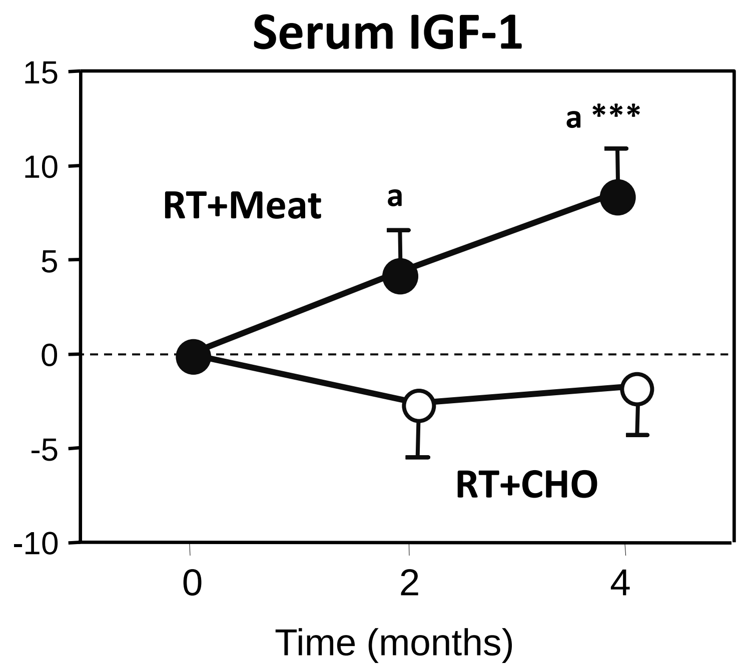
** $p<0.01$, *** $p<0.001$ vs baseline

Daly R et al. Am J Clin Nutr 2014;99(4):899-910

Protein, Exercise and Inflammation

Effects of Lean Red Meat on IGF-1 and Inflammation





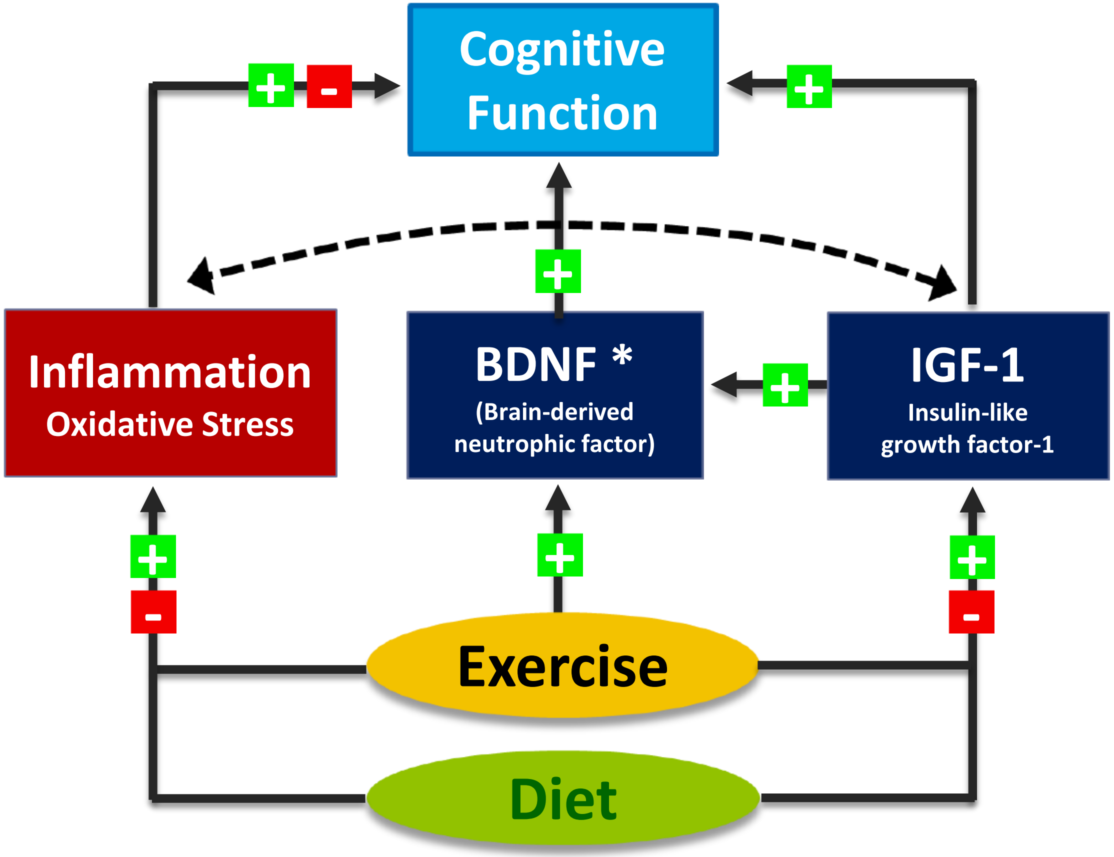
[a] P<0.05 group-by-time interaction;
*** P<0.001 within-group change relative to baseline

TNF-α decreased in the RT+meat group but not significantly different from controls. No within group changes or between group differences in IL-10, TNF-α, hsCRP or adiponectin.

Daly R et al. Am J Clin Nutr 2014;99(4):899-910

Cognitive Health and Function

Role of Exercise, Protein, IGF-1 and Inflammation



Dietary protein; energy intake; zinc; magnesium

- Increased IGF-1 levels appear to improve cognitive function.
- Declining IGF-1 levels play a significant role in the loss of mental and cognitive function frequently associated with aging.

** Brain-derived neurotrophic factor (BDNF) stimulates neurons (brain cells) to survive longer and branch and connect in new ways (synaptic plasticity) to promote memory and learning.*

Zinc, Inflammation and Health

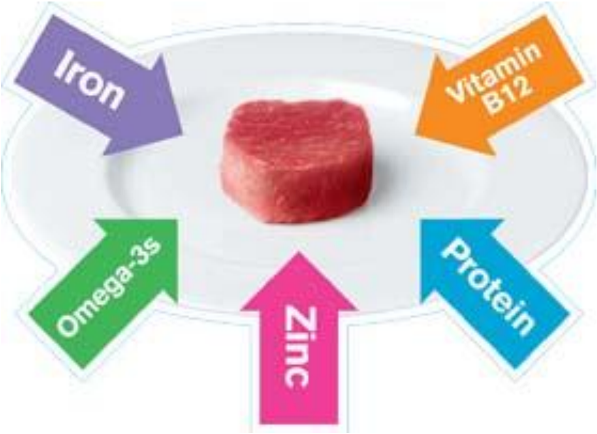
- Dietary zinc intake has been shown to be inversely associated with the levels of IL-6 and leptin in overweight/obese adults.

  Kim et al. Biol Trace Elem Res, 2014; Costarelli et al J Nutr Biochem 2010

- Zinc supplementation has been shown to decrease inflammatory markers (eg CRP and IL-6) in healthy elderly subjects and young obese women.

  Bao et al Am J Clin Nutr 2010; Kim et al. Biol Trace Elem Res, 2014

- Treatment with zinc has been associated with improved memory and cognitive function. *Maylor et al. Br J Nutr 2006*



Strategies to Prevent Inflammation

Modifiable Factors Which May Reduce Inflammation

- Exercise
- Weight loss
- Caloric restriction (not malnutrition)
- Certain diets / dietary patterns

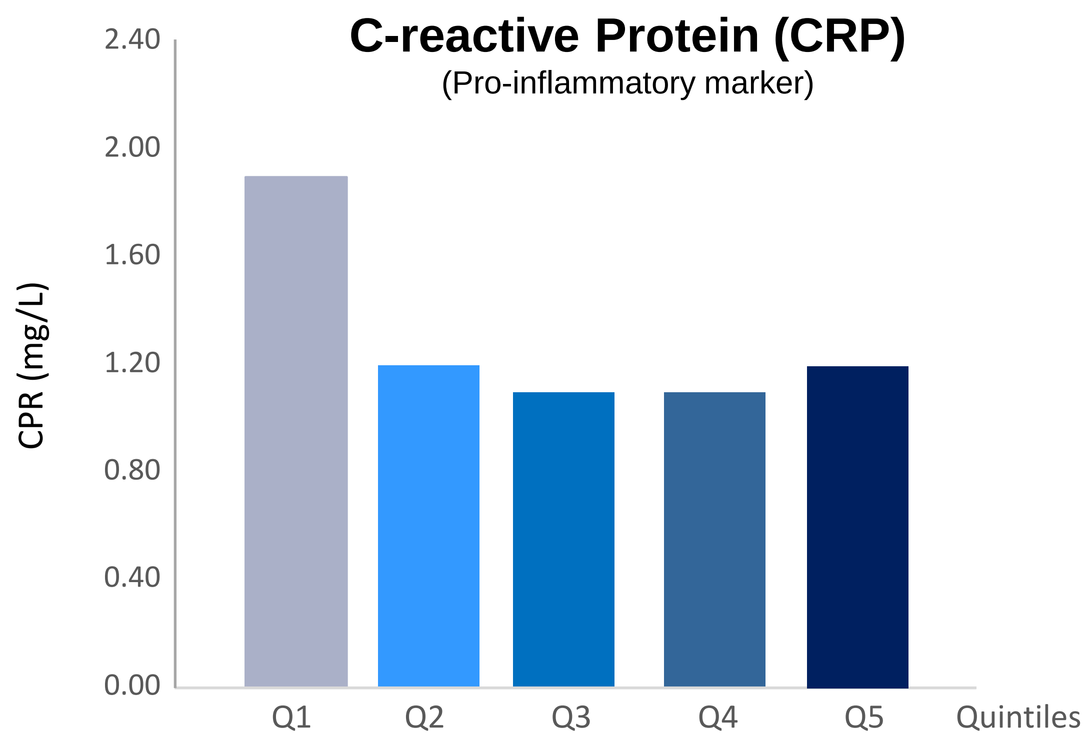
Bone and /or muscle

- Calcium / Dairy
- Vitamin D
- Protein / Soy
- Zinc and magnesium
- Vitamin K
- Omega-3 fatty acids
- Fruit and vegetables
- Polyphenols (antioxidants)

http://www.drweil.com/drw/ecs/pyramid/press-foodpyramid.html

Dietary Patterns and Inflammation

Influence of dietary patterns on CRP levels in adults aged 55+ years



Low in F&V and lean red meat and high sugar foods → Rich in F&V and lean red meat and low in high sugar foods

Wood and MacDonald. In: P Burkhardt et al (Eds). Nutritional Influences on Bone Health, 2013

Take Home Message

- **Chronic systemic low grade inflammation** is an important factor which is associated with the development and progression of many common chronic diseases.

- **Mixed findings** from human studies on the effects of individual dietary factors on inflammation and their link to bone & muscle.
  - *No single nutrient is likely to provide the optimal approach to attenuate an increase in inflammation and optimise bone and muscle health.*

- **A balanced diet** that include adequate dairy, vitamin D and protein may have beneficial effects on inflammatory markers and bone/muscle health, particularly in people with an existing chronic condition(s).
  - *Increased inflammation may alter protein metabolism and IGF-1 reducing the efficiency of dietary protein (and maybe other nutrients) to enhance muscle and bone health.*

QUESTIONS