



# Food for Thought

## Diet, BMI & MS?



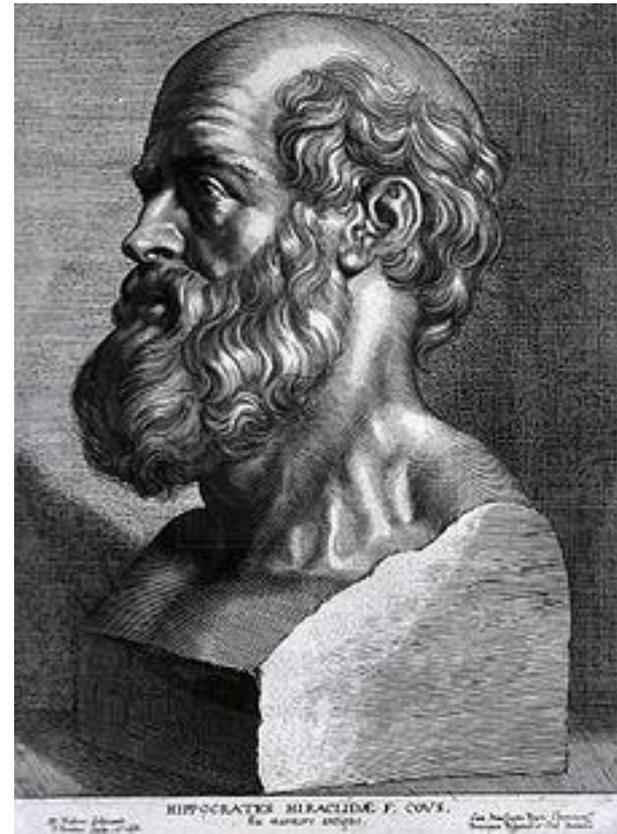
Aliza Ben-Zacharia, DrNP, ANP  
The Corinne Goldsmith Dickinson Center for MS  
The Ichan School of Medicine at Mount Sinai

# Main Questions in MS & Diet/BMI

- + Is a high BMI is associated with developing MS?
- + Is a high BMI associated with MS progression?
- + Is there any association between diet & MS?
- + Is there association between the microbiome, the diet in MS & the progression of MS?

# You Are What You Eat!

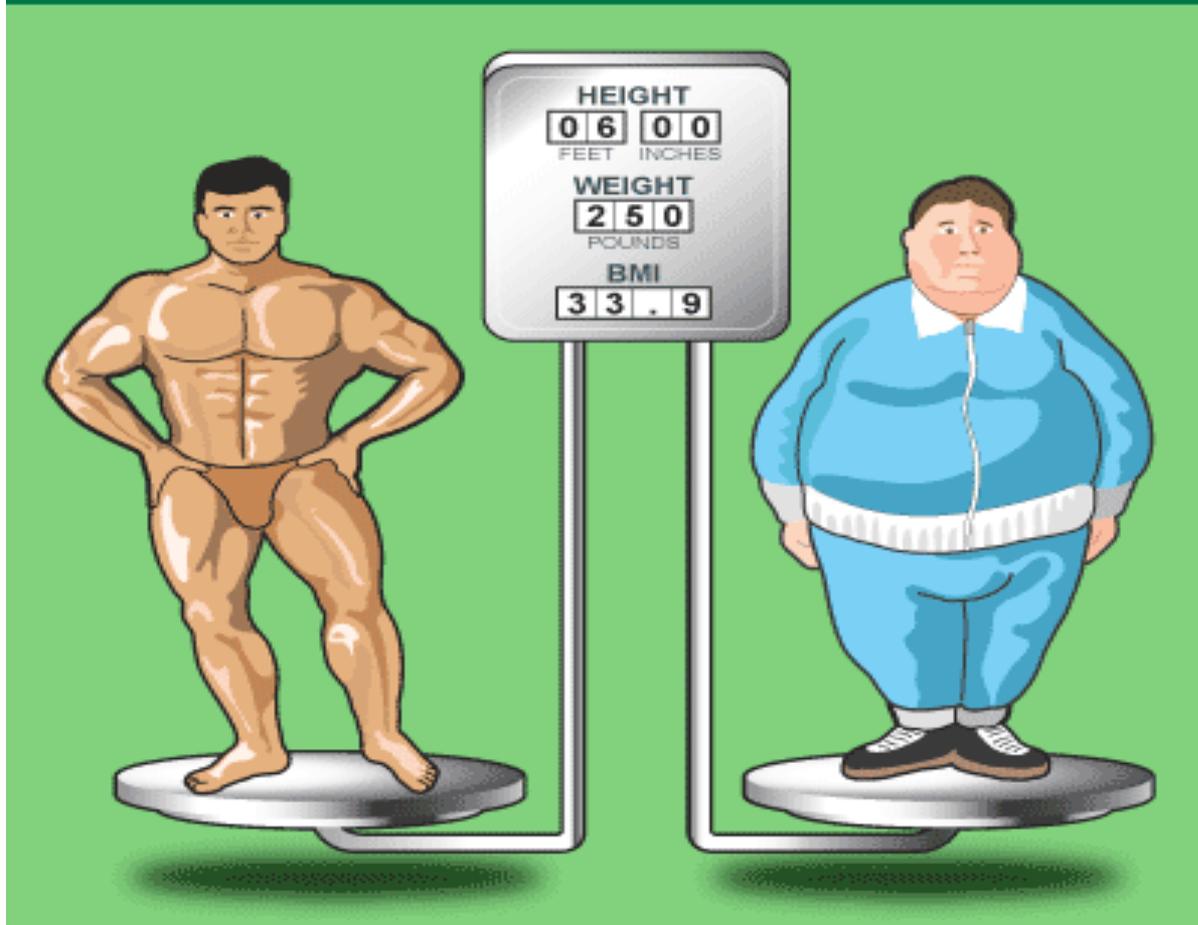
- + “Let food be thy medicine and medicine be thy food” Hippocrates
- + 1826 - Anthelme Brillat-Savarin "Dis-moi ce que tu manges, je te dirai ce que tu es." - Tell me what you eat and I will tell you what you are
- + 1863 - Ludwig Andreas Feuerbach wrote: "Der Mensch ist, was er ißt." 'man is what he eats'



# Body Mass Index (BMI) – > 25 & 30

## BMI Body Comparison

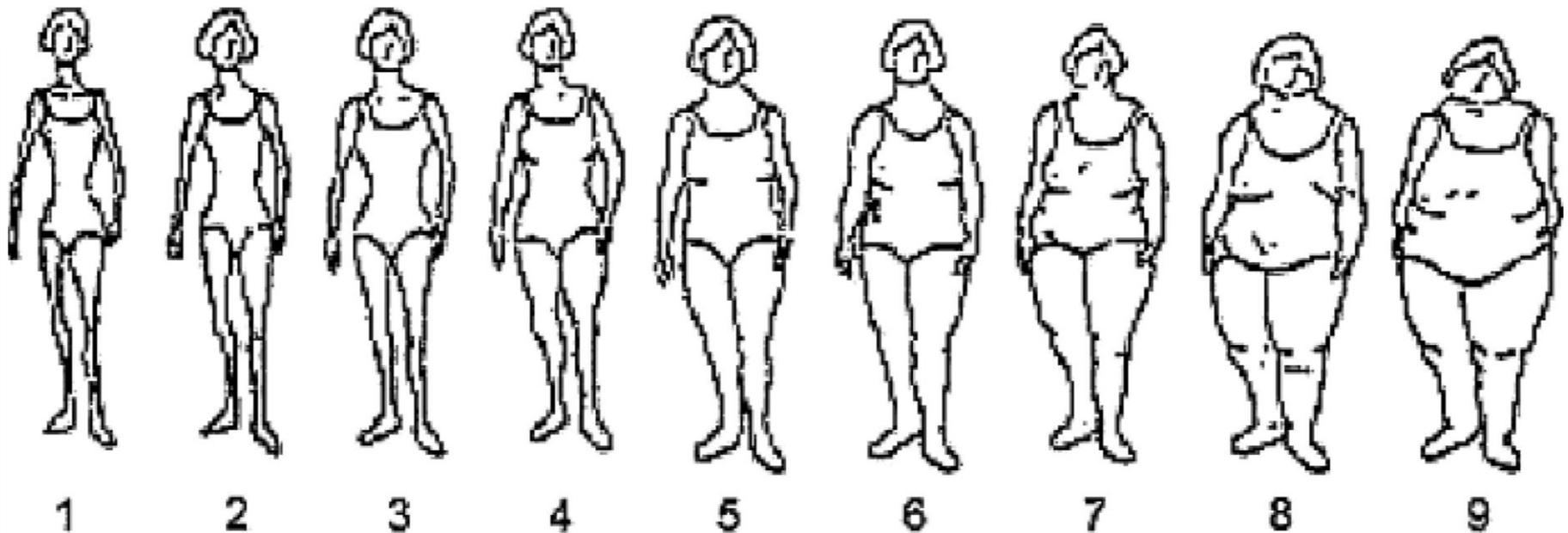
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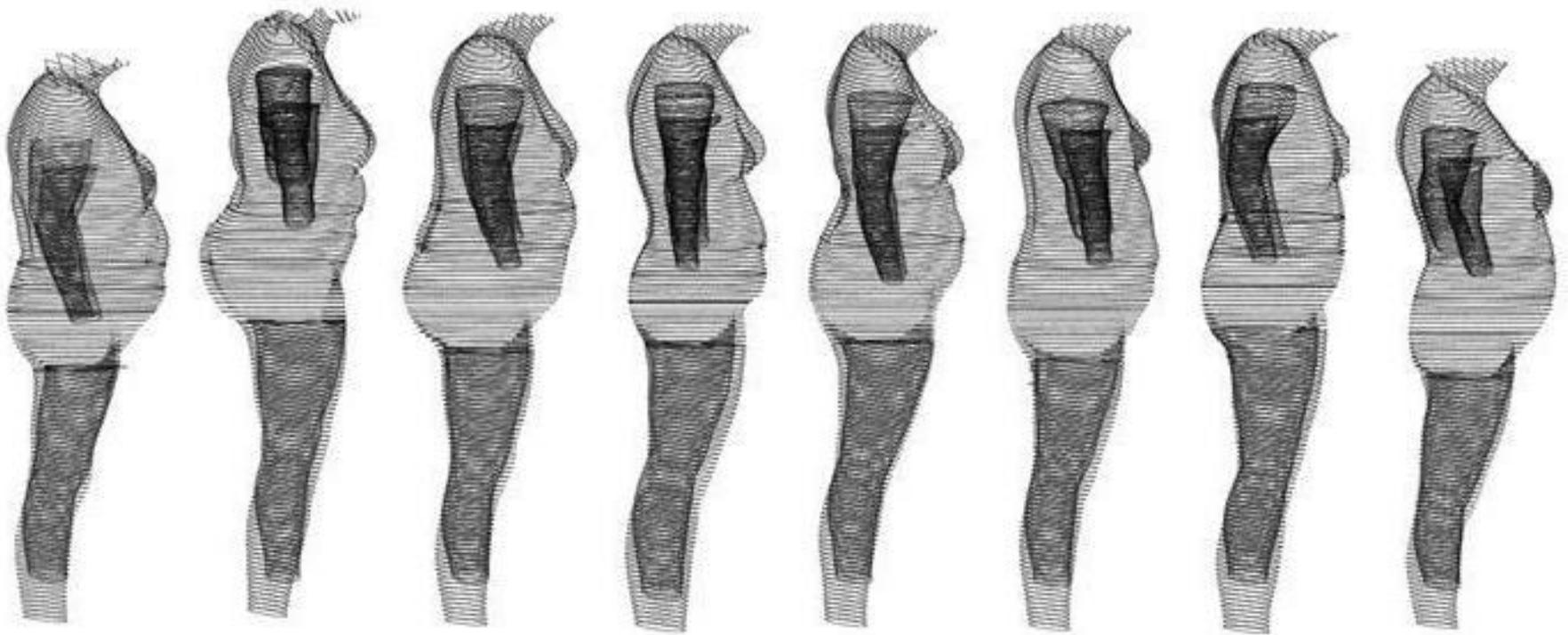
# High BMI/Obesity & Development of MS

- + **Objective:** To examine whether obesity during childhood, adolescence, or adulthood is associated with an increased risk of MS
- + **Methods**
  - + Women in the Nurses' Health Study (n 121,700) and Nurses' Health Study II (n 116,671) provided information on weight at age 18 and weight and height at baseline, from which body mass index was derived
  - + Women selected silhouettes representing their body size at ages 5, 10, and 20
  - + Over the total 40 years of follow-up in both cohorts combined, we confirmed 593 cases of MS
- + Statistical models, adjusting for age, latitude of residence, ethnicity, and cigarette smoking, were used to estimate the rate ratios and 95% confidence intervals (CI).

# Nine silhouettes women selected to best describe their body size at ages 5, 10, and 20



Those who were obese by age 18 had double the risk for MS - These illustrations represent a BMI of 30 or more



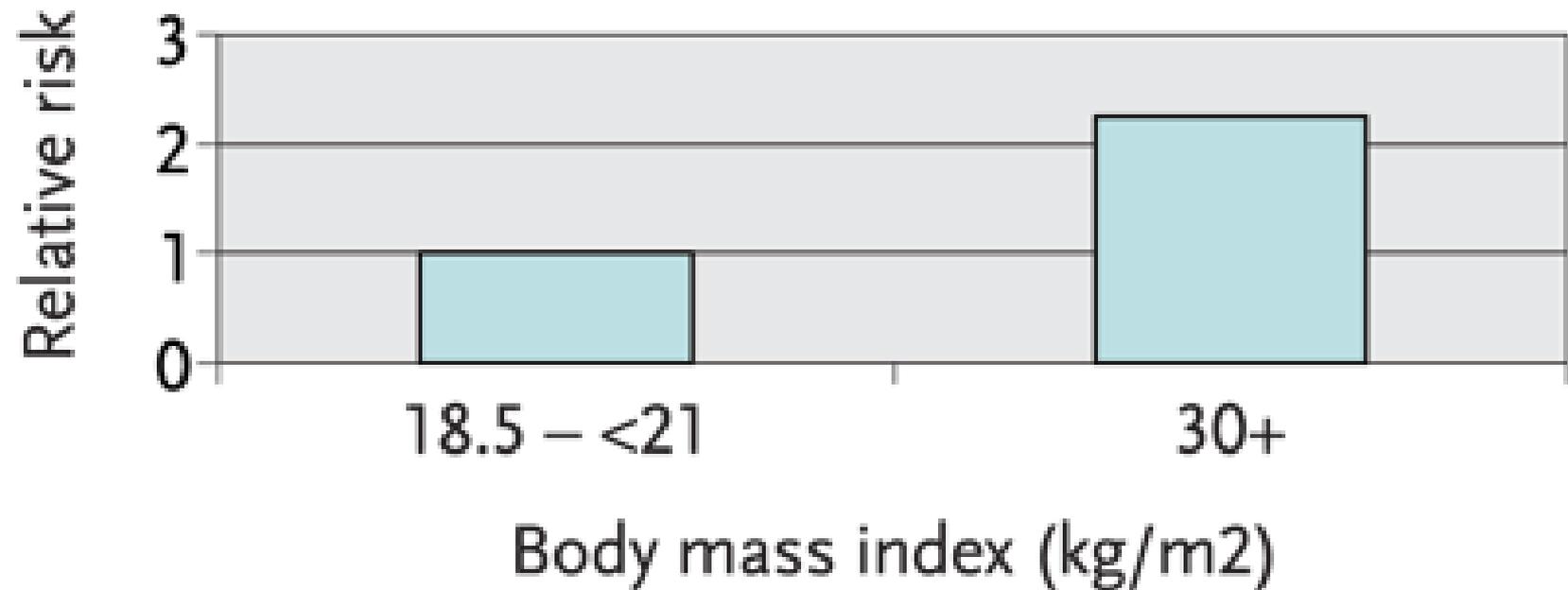
*Munger et al. Neurology*<sup>®</sup> 2009;73:1543–1550

## Nurses' Health Study (n 121,700) & Nurses' Health Study II (n 116,671)

- + Obesity at age 18 (body mass index  $\geq 30$  kg/m<sup>2</sup>) was associated with a greater than twofold increased risk of MS as compared to women with a BMI between 18.5 and 20.9 kg/m<sup>2</sup>
- + MS risk among women who were overweight, but not obese, at age 18 (BMI 25–29.9 kg/m<sup>2</sup>) was only moderately increased  
Obese adolescents have an increased risk of developing multiple sclerosis (MS)
- + The mechanisms of this association is uncertain, but this result suggests that prevention of adolescent obesity may contribute to reduced MS risk

# Obesity & Risk of MS – Nurses' Study

## OBESITY AT AGE 18 AND RISK OF MULTIPLE SCLEROSIS



*Munger et al. Neurology*® 2009;73:1543-1550

# Relative Risk of Multiple Sclerosis for Body Mass Index at Age 18 Years

+ Body Mass Index, kg/m <sup>2</sup>	Multivariate-Adjusted Relative Risk (95% CI)
+ <18.5	0.96 (0.73 – 1.27)
+ 18.5 – <21	1 [Reference]
+ 21 – <23	1.13 (0.91 – 1.40)
+ 23 – <25	0.97 (0.72 – 1.31)
+ 25 – <27	1.44 (0.87 – 2.39)
+ 27 – <30	1.40 (0.92 – 2.14)
+ >30	2.25 (1.50 – 3.37)
+ CI = confidence interval	

## Nurses' Health Study (n 121,700) & Nurses' Health Study II (n 116,671)

- + Women with a BMI  $\geq 30$  kg/m<sup>2</sup> at age 18 had a 71% increased risk of MS as compared to women with BMI between 18.5 and 20.9 kg/m<sup>2</sup>
- + As smoking was the main confounder of the association between obesity at age 18 and MS risk, we also restricted analyses to never smokers in the NHSII (there were too few never smokers in the NHS cohort to do a comparable analysis);
- + The twofold increased risk of MS persisted among never smoking women with a BMI at age 18  $\geq 30$  kg/m<sup>2</sup> (RR 2.34, 95% CI 1.21– 4.53,  $p = 0.01$ )

# BMI & Developing MS

- + In a Swedish population-based case-control study (1571 cases, 3371 controls), subjects with different BMIs were compared regarding multiple sclerosis (MS) risk, by calculating odds ratios (OR) with 95% confidence intervals (95% CI)
- + Subjects whose BMI exceeded 27 kg/m<sup>2</sup> at age 20 had a two-fold increased risk of developing MS compared with normal weight subjects
- + The obesity epidemic may explain part of the increasing MS incidence as recorded in some countries. Measures taken against adolescent obesity may thus be a preventive strategy against MS

# BMI & Progression of MS

## + OBJECTIVES:

- + To assess the potential of an online platform, PatientsLikeMe.com (PLM), for research in multiple sclerosis (MS)
- + The role of body mass index (BMI) on MS disease course was conducted to illustrate the utility of the platform

## + METHODS:

- + Compared the demographic characteristics of subjects from PLM and from a regional MS center
- + Validated PLM's patient-reported outcome measure (MS Rating Scale, MSRS) against standard physician-rated tools
- + Analyzed the relation of BMI to the MSRS measure

Bove et. Al., PLoS One. 2013;8(3):e59707.

# BMI & Progression of MS - Results

- + Compared with 4,039 MS Center patients, the 10,255 PLM members were younger, more educated
- + Disease course RRMS, with younger symptom onset and shorter disease duration.
- + MSRS scores for 121 MS Center patients revealed acceptable agreement between patient-derived and physician-derived composite scores (weighted kappa = 0.46). The Walking domain showed the highest weighted kappa (0.73) and correlation ( $r_s = 0.86$ ) between patient and physician scores.
- + Using PLM data, a modest correlation between BMI and cross-sectional MSRS ( $\rho = 0.17$ ) and no association between BMI and disease course

Bove et. Al., PLoS One. 2013;8(3):e59707.

# What is a Healthy Diet for MS?



Even Lisa is confused!

Swank Diet?

Dairy food?

Vegetarian?

Paleo Diet?

Mediterranean Diet??

Low saturated fat diet?

Gluten Free Diet?

All Raw?

# Dietary Key Points

- + Dietary changes & supplements are used by patients with MS without reliable evidence for their risks & benefits
- + Low vitamin D is associated with a worse course of disease in observational studies
- + Polyunsaturated fatty acids & a low fat diet attenuate MS immune responses in vitro & in animal studies but limited data in MS
- + Antioxidants, probiotics & vitamin B 12 supplementation attenuate MS immune response in vitro & animal models but limited data in humans
- + Milk proteins & Gluten are thought to worsen the outcomes in MS, but no randomized controlled trials re dietary restrictions

Von Gelden & Mowry, Nature Review Neurology, 2012, 8, 678-689.

# Swank Low Saturated Fat Diet

- + 144 patients with MS – DSS 4-5, ambulatory but with difficulty – fatigue & low endurance – all had ~124 g/d saturated fat
- + 70 patients – low fat diet – 20 g/d saturated fat – “Good Dieters” - overall fat consumption  $16 \pm 2.8$  g/d
- + 74 patients with MS -  $>20$  g/d saturated fat – “Poor Dieters” – overall fat consumption  $38 \pm 18$  g/d
- + Followed frequently initially = visits & then Phone FU

Swank & Goodwin, Nutrition, 2003, 19:161-162.

# Swank Low Saturated Fat Diet

- + Followed for 34 years
- + 23 deaths - 14 (20%) due to MS – in “Good Dieters”
- + 58 deaths - 48 (61%) due to MS – in “Poor Dieters”
- + 63 surviving patients continued the study up to 50 years
- + 2000 – 15 patients were seen who started the study 1950s
- + 15 patients ages 72 – 84 year old – 13 ambulatory & care for themselves & 2 with difficulty walking

Swank & Goodwin, Nutrition, 2003, 19:161-162.

# Swank Low Saturated Fat Diet

- + Low fat diet proposed by Swank – 10-15 g/d of saturated fat during 50 years study
- + 20% of patients with MS on the lowest fat diet showed little or no neurologic deterioration as a result of the progress of the disease
- + Higher percentage than the 4% of “Mild MS” cases expected within a large group of patients

Swank & Goodwin, Nutrition, 2003, 19:161-162.

# Low Saturated Fat Diet

- + Restriction of saturated fat induces remission of the disease & produces beneficial effects in MS patients
- + Saturated fat decrease membrane fluidity, lead to the synthesis of cholesterol, activate the CD14/TLR<sub>4</sub> leading to formation of TNF- $\alpha$
- + Fat influences transcriptional level, gene expression, cell metabolism & cell growth & differentiation

Swank & Goodwin, *Nutrition*, 2003, 19(5), 478

Jump & Clarke, *Annual Review of Nutrition*, 1999, 19, 63-90.

# Essential Fatty Acids & MS

- +  $\Omega$ -3 ( $\alpha$ -linoleic fatty acid) – fish oil &  $\Omega$ -6 (linoleic fatty acid) – plants
- + Hypothesis: Diet high in meat & dairy & low in fish increases the risk of MS
- + Swank 1950 – Norway – higher incidence of MS among those that had high consumption of animal fat & dairy products than fish consumption
- + No association between animal fat or saturated fat & the risk of MS – case control studies

Swank et al. NEJM, 1952, 246, 721.

Antonovsky et al. Arch. Neurology, 1965, 13, 183

# Essential Fatty Acids & MS

- + Prospective cohort study
- + The amount & type of dietary fat did not affect the risk of developing MS
- +  $\Omega$ -3 ( $\alpha$ -linoleic fatty acid) was associated with a reduced risk of MS but it did not reach statistical significance
- + No significant association between fish consumption & MS risk in one case control study but fish consumption was significantly associated with a reduced risk of MS in women

Zhang et al., Am J Epidemiology, 2000, 152, 1056.

Ghadirian et al., J. Epidemiology, 1998, 27, 845

# Polyunsaturated Fatty Acids (PUFA)

- + Nordvik – fish oil supplements & progression of MS in 16 newly diagnosed patients – significant reduction in relapse rate and improvement on EDSS
- + Weinstock-Guttman – low fat diet supplemented with  $\Omega$ -3 PUFA has moderate benefits in RRMS but the potential therapeutic effects may be related to the low fat diet
- + Increased intake of  $\Omega$ -3 fatty acids reduce the synthesis of pro-inflammatory leukotriene B<sub>4</sub> and prostaglandin E<sub>2</sub>

Nordvik et al., *Acta Neurol Scand.* 2000, 102, 143.

Weinstock-Guttman et al., *Prostaglandins Leukot. Essent. Fatty Acids*, 2005, 73, 397.

Calder P.C. *Trends Immunol. Today*, 1998, 6, 244. James et al., *Am J. Clin. Nutr.*, 2000, 71, 343S.

# Omega-3 Fatty Acids



- + There is evidence that omega-3 fatty acids reduce the risk of cardiovascular events
- + There is not enough definite proof available to recommend omega-3 fatty acids for MS, but findings suggest beneficial effects from unsaturated fatty acids
- + Justifiable to consume foods rich in omega-3 fatty acids, high-quality vegetable oils (containing high amounts of unsaturated fats), and 2 or more seafood meals per week

# Consumption of milk & MS

- + High consumption of milk was associated with increased incidence of MS
- + The incidence of MS in Japan rose between the years 1950 – 1969 in parallel with increased consumption of milk
- + Meat & dairy products were associated with incidence of MS in the USA

Schwarz & Leweling, *Multiple Sclerosis*, 2005, 11, 24-32.  
Butcher. *N Z Medicine J*, 1976, 83, 427-430.

# Cow Milk – Saturated Fat

- + Milk proteins with effect in MS are the proteins of the milk fat globule membrane (MFGM proteins)
- + The most representative of MFGM is Butyrophilin (BTN)
- + BTN is similar to MOG (myelin oligodendrocyte glycoprotein)
- + BTN blocks MOG-induced EAE but also induces inflammatory responses in the CNS
- + Antibody cross-reactivity between MOG & BTN has been observed in MS

Riccio et al., Autoimmune Diseases, 2010.

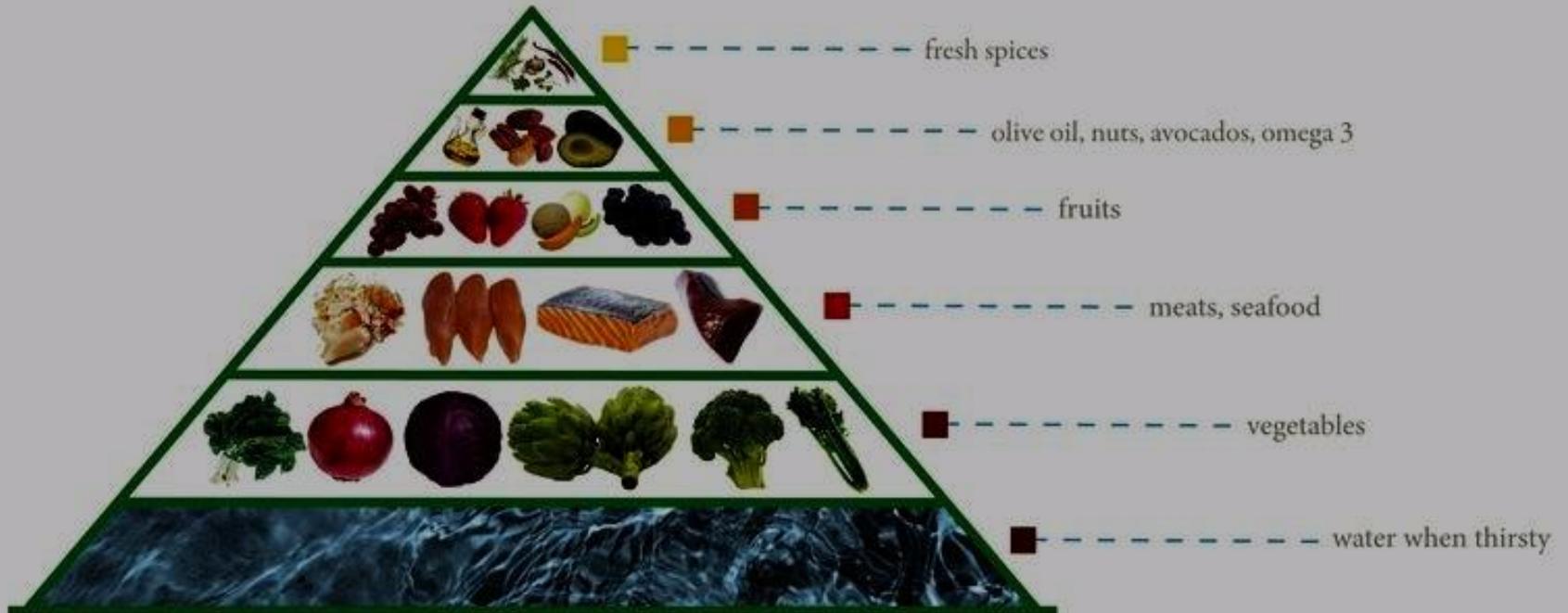
# Gluten Free Diet & MS

- + Open label trial
- + End Points: ARR, EDSS
- + 42 patients on a gluten free diet
- + Results
  - + No change in relapse rate
  - + No change in disease progression based on EDSS

Liversedge, L. British Medical Bulletin, 1977, 33, 78-83.

# Paleo Diet Food Pyramid

## The New Evolution Diet Food Pyramid



# Vitamin D & MS

- + Studies indicate that vitamin D alters immune function in a way that may be desirable in MS
- + Many people with MS have risk factors for developing osteoporosis:
  - + Female gender, decreased physical activity, decreased exposure to sunlight, and frequent treatment with steroids
- + People who have these risk factors may consider supplements of vitamin D and calcium
- + Recommended intake of vitamin D is based on blood test level

# Vitamin D & MS

- + Double blind placebo controlled randomized trial
- + End Points: ARR, EDSS, MSFC
- + 35 patients received vitamin D<sub>3</sub> 20,000 IU weekly vs. 33 patients getting placebo
- + Results
  - + No change in relapse rate or EDSS score

Kampman et al., Multiple Sclerosis, 2012, 18, 1144-1451.

# Vitamin D - Nurses' Study

- + Nurses' Health study (20yrs) and Nurses' Health study II (10yrs) – 40% reduced risk of MS found in women in the highest quintile of vitamin D intake compared with those in the lowest quintile
- + Vitamin D supplementation showed correlation with increased risk of development of MS
- + Vitamin D deficiency may lead to increased intensity of the symptoms in MS due to enhancement of inflammatory cytokines
- + Polymorphisms in certain genes for the vitamin D receptor have been associated with increased likelihood of MS

# Vitamin B<sub>12</sub> & MS

- + Vitamin B<sub>12</sub> is a prerequisite for the synthesis of myelin
- + Vitamin B<sub>12</sub> & MS share clinical & MRI characteristics
- + High dose therapy with vitamin B<sub>12</sub> over 6 months trial in 6 severely disabled patients with MS – no clinical benefit
- + Placebo control trial with 138 patients – small without significance - beneficial effect of parenteral therapy of vitamin B<sub>12</sub>
- + No scientific basis to recommend vitamin B<sub>12</sub> supplementation unless has deficiency

Schwarz & Leweling, *Multiple Sclerosis*, 2005, 11, 24-32.

Kira et al., *Internal Medicine*, 1994,33, 82-86.

Wade et al., *J neurol Neurosurg Psychiatry* 2002, 73, 246-249.

# Probiotics & MS

- + Open label single blind trial
- + Primary end point: Gadolinium enhancing lesions on MRI
- + Secondary end point: serum cytokine levels (IL<sub>4</sub>, IL<sub>10</sub>, IL<sub>17</sub>)
- + Results:
  - + RRMS - naive patients - Decreased numbers of lesions on GAD MRI as compared to pre study
  - + Increased levels of IL<sub>4</sub> & IL<sub>10</sub>
- + Administration of probiotics to Mice EAE model
  - + Reduction in IL<sub>17</sub> & increased IL<sub>10</sub>

Von Gelden & Mowry, Nature Review Neurology, 2012, 8, 678-689.

# Uric Acid – BBB Integrity

- + Study Design: Double blind placebo controlled randomized – 16 patients with RRMS taking inosine for 12 months vs. 6 months of placebo followed by 6 months of inosine
- + End Points: RR, EDSS, MRI
- + Results:
  - + Decreased number of Gad enhanced lesions seen on MRI
  - + Decreased EDSS score

# Uric Acid & MS

- + Study Design: Multicenter - Double blind placebo controlled randomized – 159 patients – inosine vs. placebo as add on to IFN- $\beta$
- + End Points:
  - + Primary: change in EDSS at 24 months
  - + Secondary: time to confirmed disability progression, time to first relapse, mean EDSS change, ARR, MSFC & number of relapses
- + Results:
  - + No change in in relapse rate
  - + No change in EDSS scores

Gonsette et al., Multiple Sclerosis, 2010, 16, 455-462.

## 2 Cochrane Review – 2012

- + Attempt to answer patients' questions about dietary recommendations and their impact of prognosis for people with MS
- + Selection criteria limited to MS and trials that had a comparison arm
- + Results:
  - + No specific recommendation for diet & supplements – adopt healthy eating habits
  - + PUFAs seem to have no effect on disease progression & the risk of clinical relapses over 2 years
  - + Low level of vitamin D is associated with lower subsequent disability – authors noted no cause-effect relationship

Farinotti et al., Cochrane Database Syst Rev. 2007 Jan 24;(1):CD004192.

## Guts, bugs and MS

### Did you know that...

- We are made up of more microbes than human cells?
- Bacteria account for 1-3% of body mass?
- Only 1% of bacteria can be cultured in the lab?
- Most bacteria are non-pathogenic?
- There are more bacterial than human genes?



# Relationship between Microbiome, Diet & MS

- + The link between dietary intake and host immune system is not direct, but mediated by the commensal bacteria residing in the walls of the intestine called the microbiome
- + Commensal bacteria can be classified based on their unique DNA sequences
- + Commensal bacterial – responsive for dietary manipulations, regulating metabolism, nutrient absorption and modulation of immune activity
- + The importance of the intestinal microbiome & its interactions with the immune system are recognized with regard to the development of autoimmune diseases

<http://blog.mountsinai.org/blog/exploring-the-role-of-microbiome-in-multiple-sclerosis/>

# Known Core & Number of Species

- + Lactobacillus lactis 1
- + Lachnobacterium spp. 1
- + Lachnospira pectinoschiza 1
- + Parabacteroides spp. 3
- + Prevotella spp. 2
- + Roseburia intestinalis 1
- + Ruminococcus spp. 13
- + Streptococcus spp. 18
- + Subdoligranulum variabile 1
- + Sutterella wadsworthia 1
- + Uncultured Phylotypes 387
- + Akkermansia muciniphila 1
- + Alistipes finegoldii 1
- + Anaerotruncus colihominis 1
- + Bacteroides spp. 11
- + Bifidobacterium spp. 2
- + Clostridium spp. 13
- + Colinsella spp. 2
- + Dorea spp. 2
- + Eubacterium spp. 9
- + Faecalibacterium prausnitzii 1

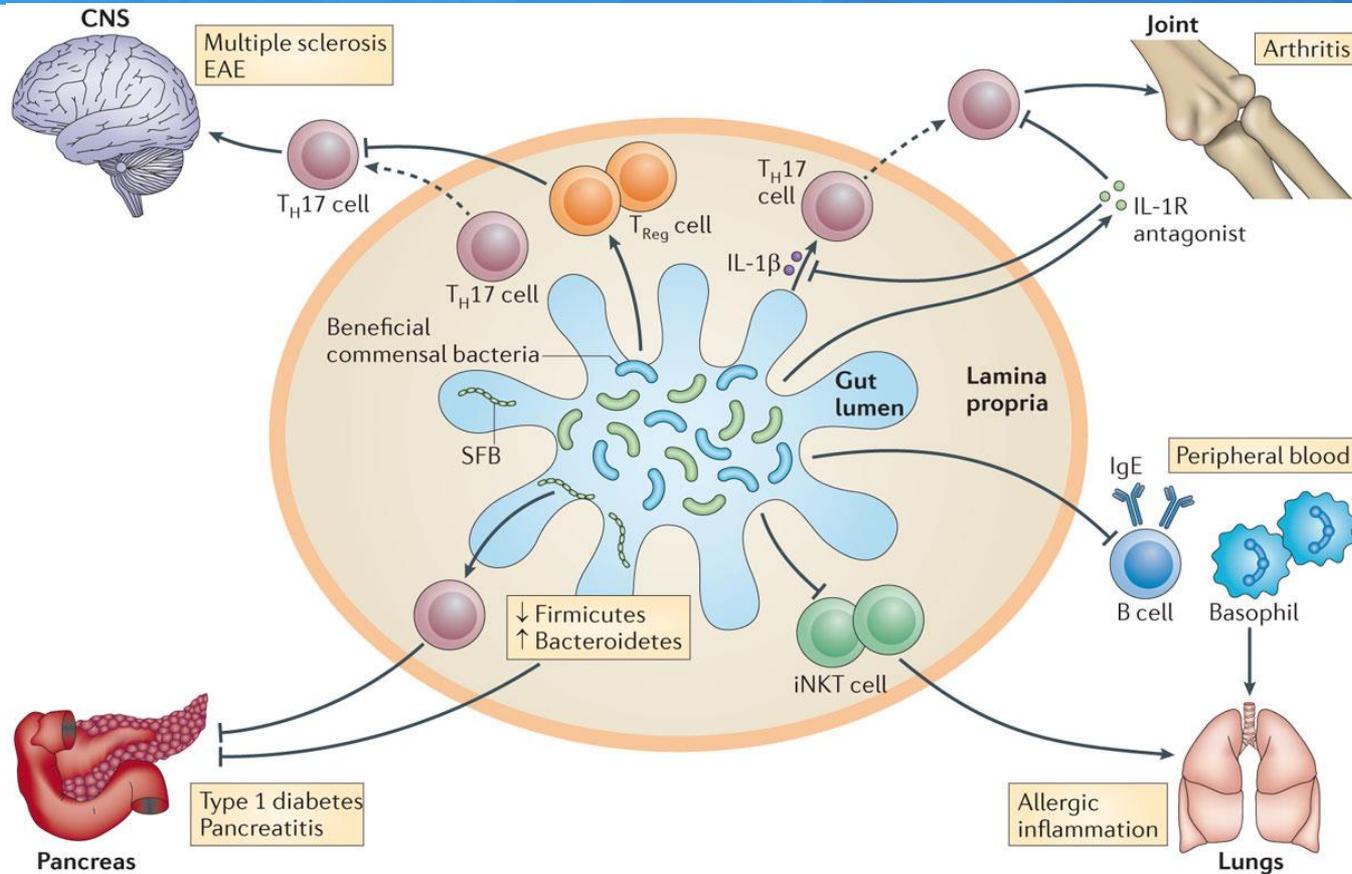
# Diet & Microbiome effects on MS

- + Rise in the incidence of Japanese patients developing RRMS was associated with “Westernized” dietary habits
- + EAE models suggest that the gut flora contribute to the development of disease
- + Sterilization of the gut by treatment with a mixture of antibiotics reduced the severity of EAE

Kira et al. (1999) Changes in the clinical phenotypes of multiple sclerosis during the past 50 years in Japan. *J Neurol Sci* 166:53–57

Ochoa-Repáraz et al (2009) Role of gut commensal microflora in the development of experimental autoimmune encephalomyelitis. *J Immunol* 183:6041–6050

# Microbiome & extra-intestinal autoimmune diseases



Kamada et al., Nature Reviews Immunology 13, 321-335 (May 2013)

# Summary

## No specific diet has proven beneficial in MS

- + Principles of healthy diet
- + No basis for recommendations to avoid particular foods (e.g., alcohol, meat, wheat/gluten, coffee, animal fat, dairy products)
- + Low saturated fat
- + Fish or Omega 3 supplementation
- + Probiotics / Vitamin D



Thank You!  
Questions / Comments

