WEBINAR & TELELEARNING SERIES

Diet & MS:
A Neurologist's Perspective

November 8, 2016

Presented by:

ABOVE MS™ Brought to you by Biogen

EMD SERONO

Teva Pharmaceuticals | Acorda Therapeutics

Mallinckrodt Pharmaceuticals Autoimmune and Rare Diseases | US Bank

United Way of Eagle River Valley


Thank you
for joining
Can Do MS and
the National MS
Society tonight!
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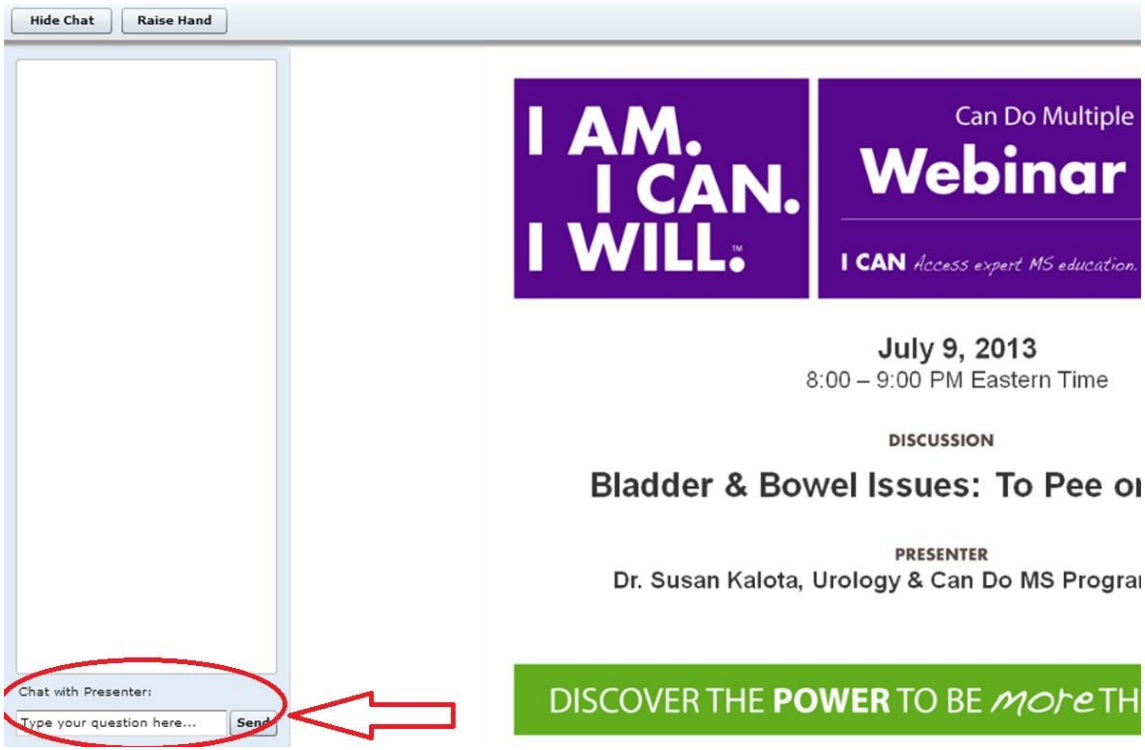
- **Chat Feature** – Type in your questions using the chat box on the lower left hand side of your screen.



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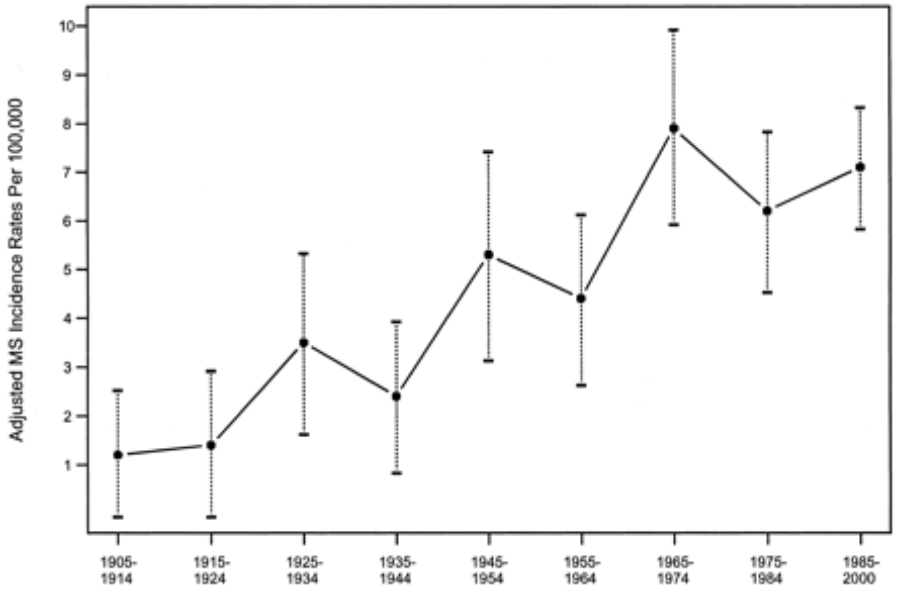
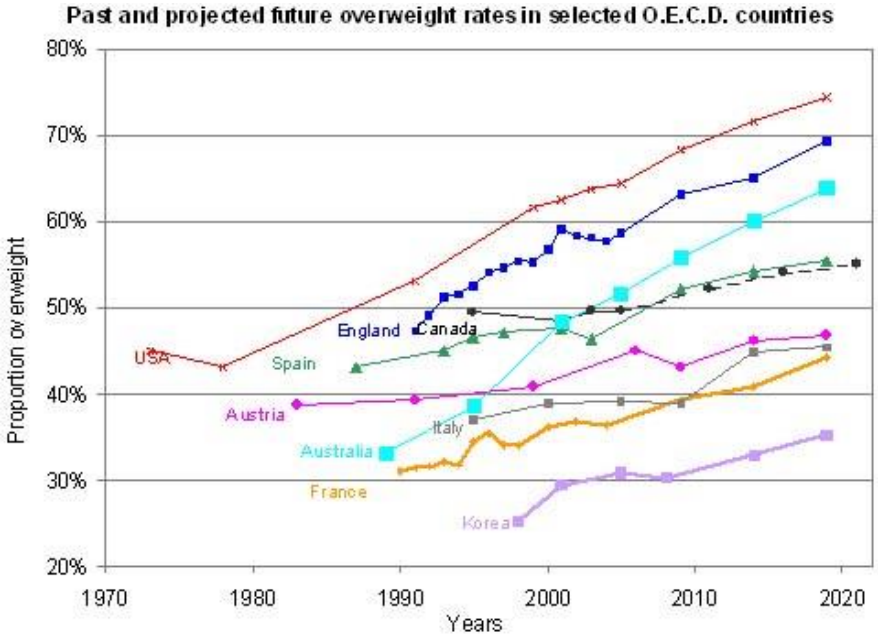
Why study the effect of diet in MS ?

Why study the effect of diet in MS ?

MS prevalence continues to rise…



Minnesota, 1905-2000



…as does the prevalence of obesity

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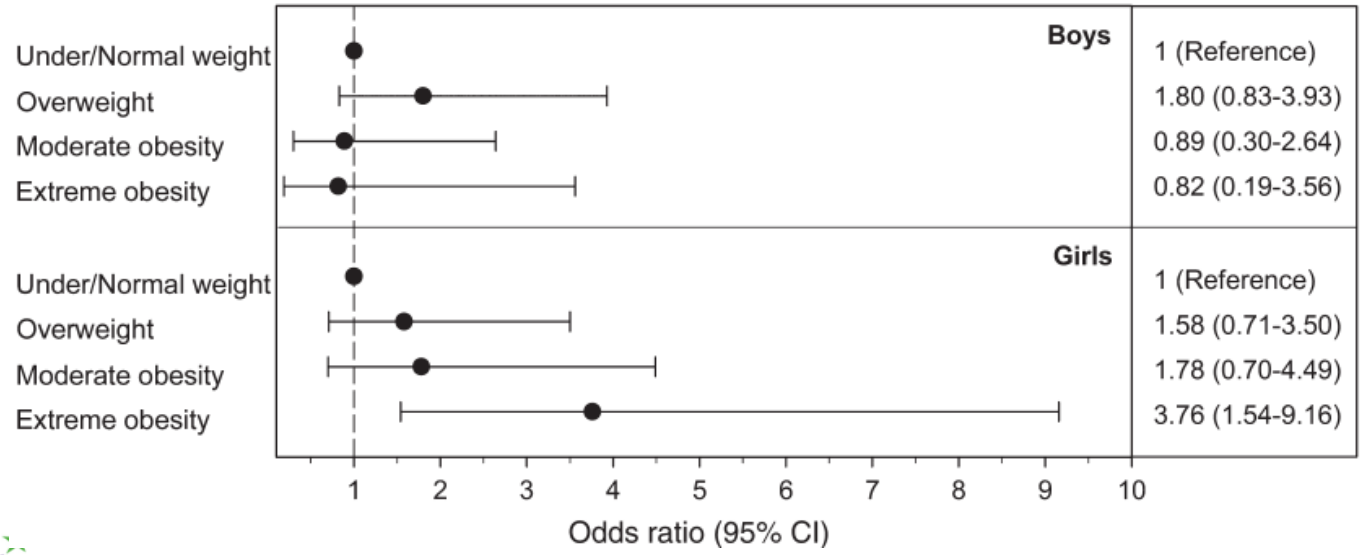
Obesity is a risk factor for MS

Obesity at age 18/20 is linked to increased MS risk (Munger, 2009)

Higher BMI at ages between 7 to 13 linked to increased MS risk

Figure Association between weight class and pediatric multiple sclerosis/clinically isolated syndrome by sex



Langer-Gould et al., Neurology 2013

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How Might Diet Influence MS Risk or Prognosis?

Direct effects on the immune system

- metabolism of immune cells can influence their function
- immune cells have receptors for Vitamin D, fatty acids

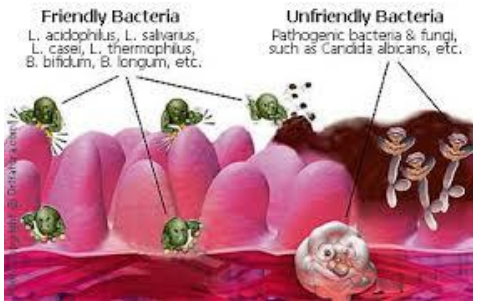
Altering the gut microbiota

- gut bacteria may be associated with MS
- diet can alter the gut bacterial composition

Effects on components of the central nervous system

- certain foods might be protective for cells in the CNS

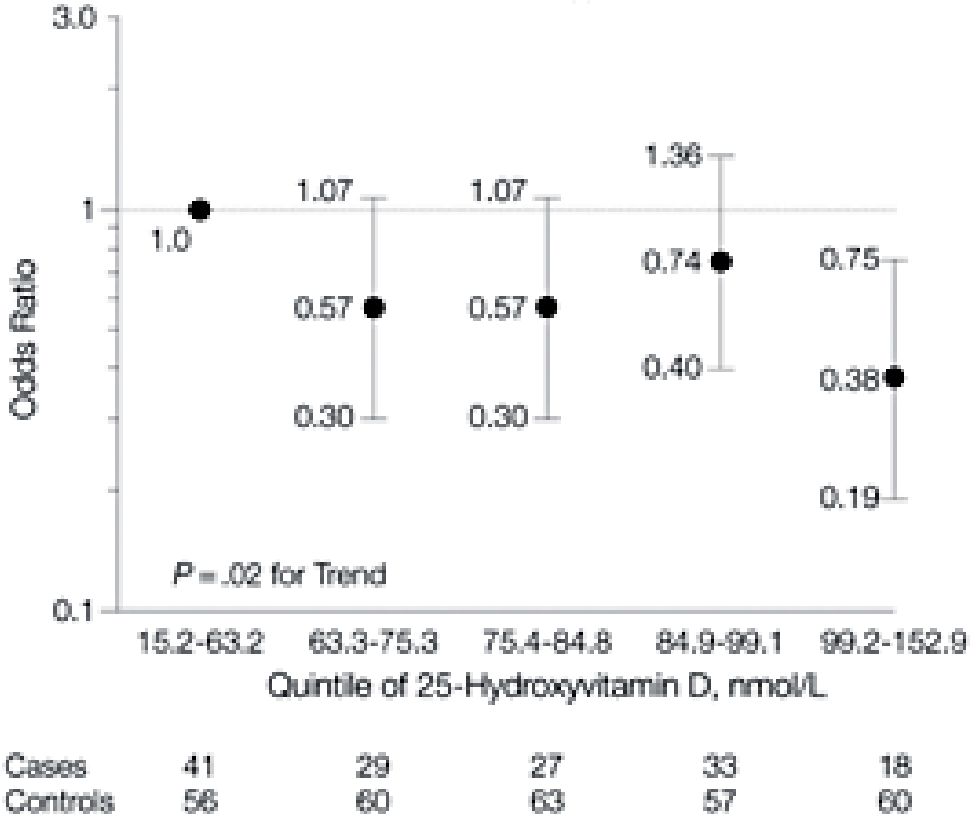
Gut Bacteria



- 100 Trillion bacteria in the intestines
- Normal bacteria help to “teach” the immune system what belongs and what is an invader
- Altered [numbers or types of] bacteria → increase risk of some autoimmune diseases, asthma
- Changes in bacteria may be due to dietary changes, use of antibiotics

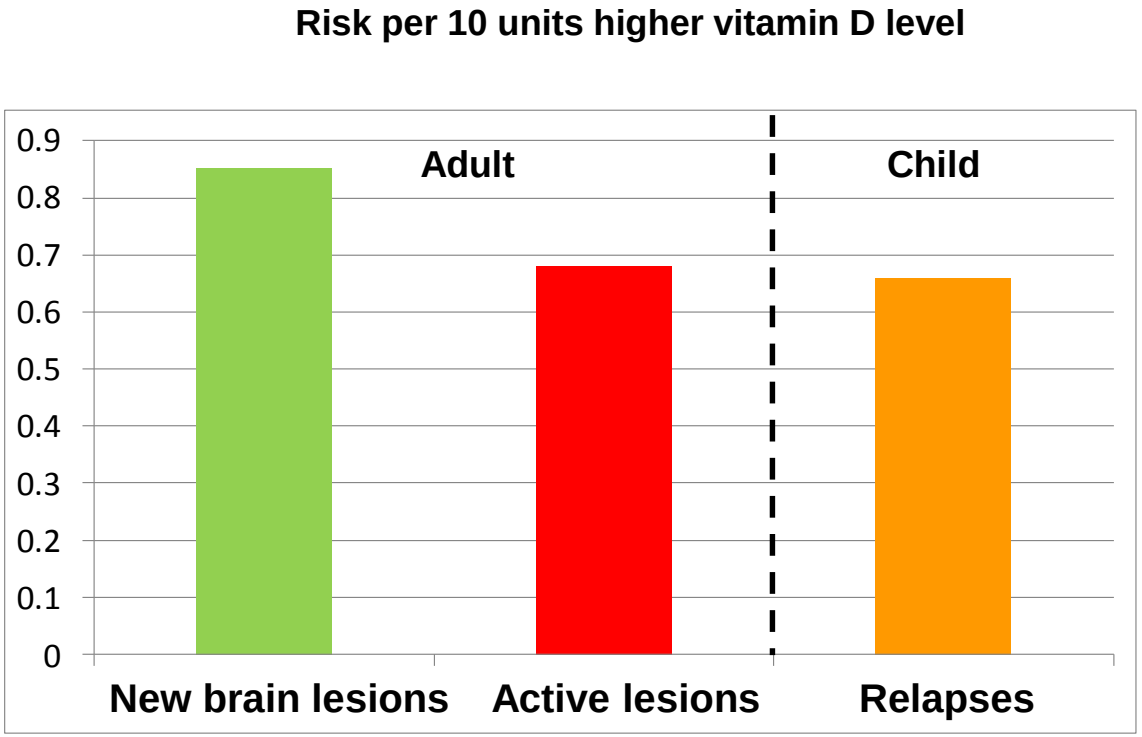
Vitamin D

Vitamin D Levels and MS Risk



Munger et al, JAMA 2006

Higher vitamin D levels → Less MS activity



Slide courtesy : Ellen M. Mowry MD, MCR

Mowry EM, Annals of Neurology 2010, 2012

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Scientific “Levels of Evidence”

Example

To prevent “chicken or the egg” problem and other major bias

Level I: Well-designed, randomized controlled trial

Level II-1: Well-designed trial without randomization

Level II-2: Cohort/case-control study

Level II-3: Comparing times (or places) with and without the intervention

Level III: Opinions of experts, committees, etc.

Why Are Impacts of Diets and Supplements Reported by Media So Confusing?

Vitamin D and MS

Example 1.

We think:

Low vitamin D ⟶ MS risk ⟶ Worse outcomes for people who already have MS

What if:

More severe MS → less time in sun → low vitamin D

Example 2.

People with lower vitamin D levels also have lower levels of …. (sodium, zinc, chocolate intake)

AND

Chocolate intake → improved MS

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Cautionary Lessons from Supplements for Other Diseases

	Folic Acid	Beta Carotene
Observational (overall population)	↓ Colon cancer	↓ Heart disease
Randomized Trial (at-risk populations)	↑ Advanced pre-cancerous colon lesions	↑ Lung cancer ↑ Heart disease deaths

Recent results from vitamin D trials

SOLAR trial

- 14,000 IU cholecalciferol vs placebo for 48 weeks in addition to Interferon
- Enrolled 229 patients of whom 81% completed the study.
- There was a 31% reduction in new MRI lesions over the study period

French trial

- 100,000 IU cholecalciferol twice monthly for 2 years in 129 patients
- 20% reduction in relapse rate in the entire population
- In completers there was a significant reduction in relapses (60% lower) and new MRI lesions (almost 80% lower)

Hupperts R et al. ECTRIMS 2016.
Camu W et al. ECTRIMS 2016.

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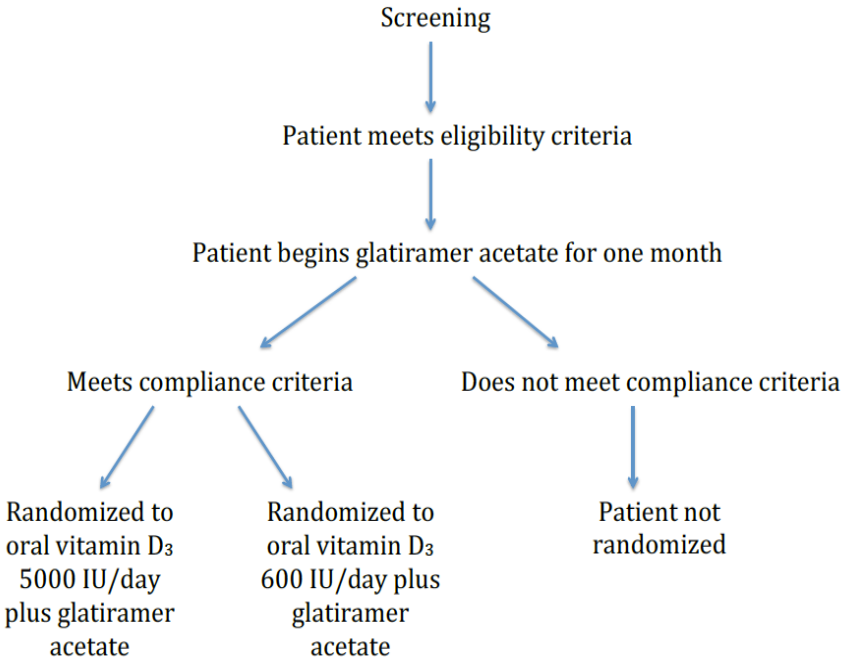
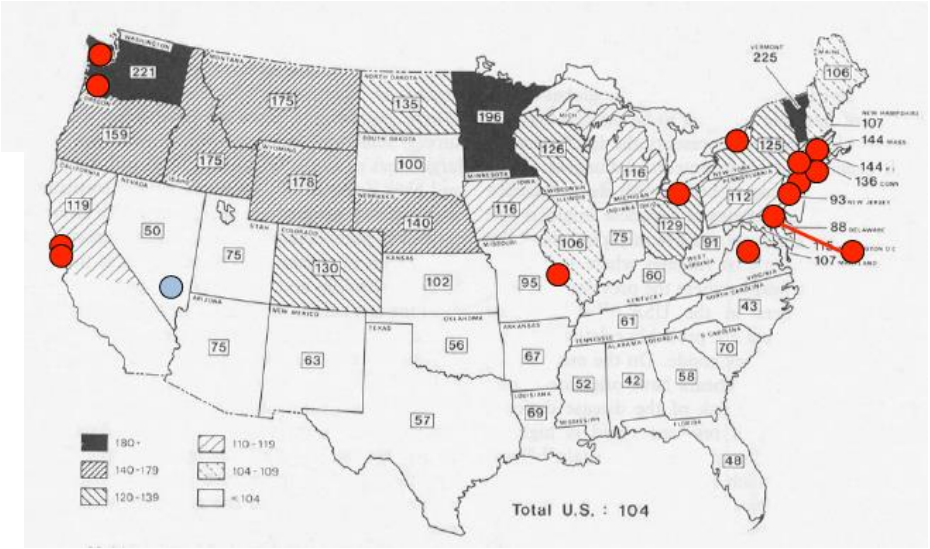
VIDAMS trial

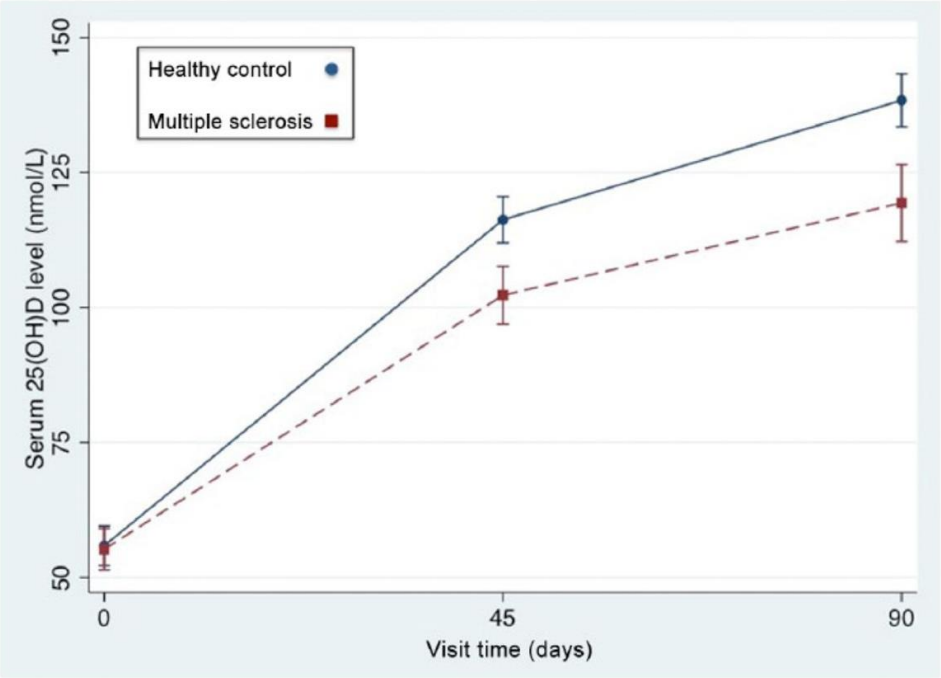




Bhargava P et al. Contemp Clin Trials. 2014 Nov; 39(2): 288-93.

MS patients have a diminished response to vitamin D supplementation compared to healthy individuals

Characteristic	Multiple Sclerosis (n=27)	Healthy controls (n=30)	p-value
Age (years)	40.2 ± 9.2	37.9 ± 12.1	0.44
Body mass index (kg/m^2)	25.3 ± 2.9	23.6 ± 2.9	**0.03**
Serum 25-hydroxyvitamin D (ng/mL)	22.1 ± 7.9	22.4 ± 8.0	0.91
Calcium (mg/dL)	9.3 ± 0.3	9.5 ± 0.3	0.14
Oral contraceptive use (n(%))	4 (14.8)	9 (30)	0.17
Dietary vitamin D intake (IU/day)	117.8 ± 184	77.3 ± 97	0.31
Fat Intake Score	18.1 ± 7.9	19.1 ± 6.6	0.61
Sun exposure (hours per week)	12 ± 10.6	9.3 ± 5.8	0.23



Bhargava P et al. Mult Scler. 2015.

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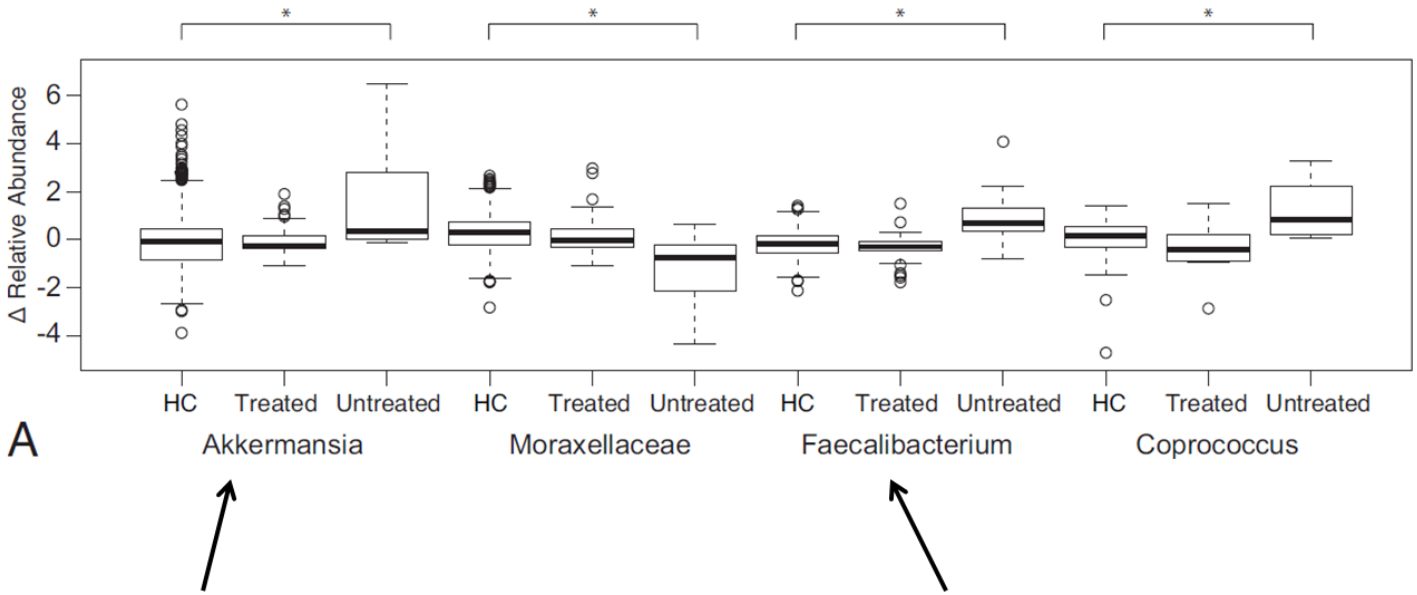
Vitamin D supplementation also affects the gut microbiome



Involved in "immune tolerance"

Prevents inflammation

Cantarel BL et al. Journal of Investigative Medicine, 2015

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Summary

- Vitamin D deficiency: increased risk for MS and with worse disease activity in established MS.
- Optimal dose of vitamin D and effect on clinical disease activity are being investigated
- Results from ongoing trials suggest decreased radiological disease activity with high-dose vitamin D supplementation.
- MS patients may not have the same response to vitamin D supplementation as healthy controls.

Polyunsaturated fatty acids (PUFAs)

PUFAs

- Derived from both plant and animal sources
- PUFAs contain 2 or more double bonds beginning at the third or sixth carbon (ω-3 or ω-6)
- They are involved in the biogenesis of multiple inflammatory molecules both anti- and pro-inflammatory
- Various immune cell populations have receptors for PUFAs

PUFAs and MS risk

- Women in the “Nurses Health Study” and “Nurses Heath Study II” were included and data on diet was derived from a standardized questionnaire

- Higher baseline PUFA intake was associated with 34% lower MS risk

- Higher linoleic and linolenic acid intake was associated with lower MS risk

Bjornevik K et al. ECTRIMS 2015.

PUFAs and MS risk

- Case-control study from Australia included 267 cases and 517 controls

- Higher intake of ω-3 PUFA (39% lower) especially those from fish (46% lower) associated with lower risk of MS

(a)	Q1	Q2	Q3	Q4	Q5	*p* for trend
Total fat						0.54
Cases/controls	62/103	53/103	52/104	43/103	57/104	
Median (range)	38 (13–47)	55 (47–60)	67 (60–75)	85 (76–97)	122 (98–559)	
AOR (95%CI)	1.00	0.83 (0.49–1.41)	0.83 (0.46–1.49)	0.65 (0.32–1.35)	1.00 (0.38–2.66)	
Saturated fat						0.36
Cases/controls	57/103	51/103	58/104	41/103	60/104	
Median (range)	15 (5–18)	22 (18–24)	28 (25–32)	35 (32–41)	51 (41–224)	
AOR (95%CI)	1.00	0.92 (0.54–1.55)	1.22 (0.70–2.12)	0.92 (0.47–1.79)	1.86 (0.79–4.35)	
MUFA						0.32
Cases/controls	69/103	49/103	49/103	43/103	57/104	
Median (range)	14 (5–17)	19 (17–21)	23 (21–27)	30 (27–35)	44 (35–213)	
AOR (95%CI)	1.00	0.82 (0.47–1.41)	0.73 (0.41–1.31)	0.61 (0.30–1.23)	0.87 (0.33–2.31)	
PUFA						0.18
Cases/controls	56/103	60/103	58/104	44/103	49/104	
Median (range)	4 (1–6)	7 (6–8)	10 (8–11)	13 (11–15)	18 (15–84)	
AOR (95%CI)	1.00	1.11 (0.65–1.90)	1.06 (0.59–1.89)	0.68 (0.37–1.27)	0.74 (0.34–1.57)	
Omega-3 PUFA						0.02
Cases/controls	60/103	58/103	58/104	50/103	41/104	
Median (range)	0.7 (0.2–0.9)	1.0 (0.9–1.1)	1.3 (1.1–1.4)	1.7 (1.4–2.0)	2.4 (2.0–16.9)	
AOR (95%CI)	1.00	1.09 (0.64–1.86)	0.81 (0.45–1.46)	0.60 (0.31–1.16)	0.38 (0.16–0.88)	
Omega-6 PUFA						0.30
Cases/controls	51/103	65/103	54/104	47/103	50/104	
Median (range)	3.7 (0.9–4.7)	6.0 (4.8–7.1)	8.0 (7.1–9.3)	10.6 (0.3–12.2)	15.3 (12.3–66.9)	
AOR (95%CI)	1.00	1.29 (0.75–2.20)	1.02 (0.57–1.81)	0.82 (0.44–1.55)	0.83 (0.39–1.75)	

Hoare S et al. Mult Scler. 2016.

Studies of PUFA and PUFA rich diets in MS

- Trial of low-fat diet supplemented with ω-3 PUFAs (fish-oil) compared to olive oil supplemented diet in 31 patients. There was an improvement in quality of life scores and a reduction in relapse rate compared to pre-diet disease activity.

- OFAMS trial tested two PUFAs (EPA + DHA) in addition to interferon in 46 patients in each arm – no change in MRI or clinical disease parameters over the course of the study.

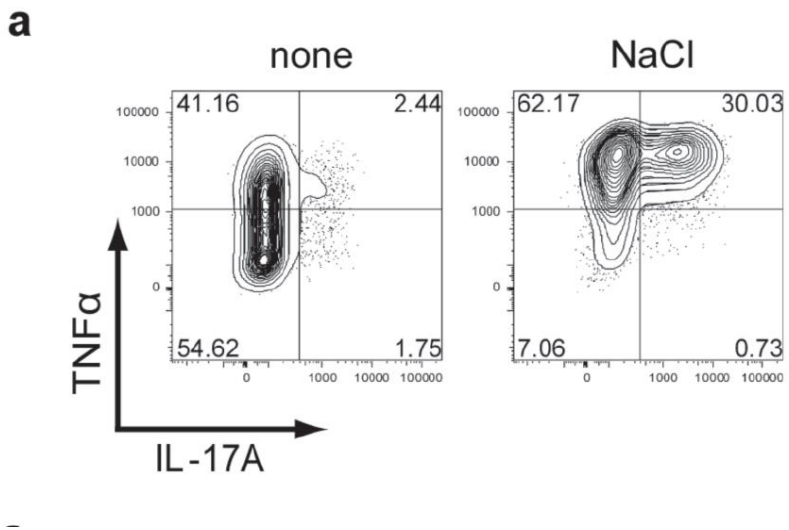
Weinstock-Guttman B et al. Prostaglandinds Leukot Essent Fatty Acids. 2005
Torkildsen O et al. Arch Neurol. 2012

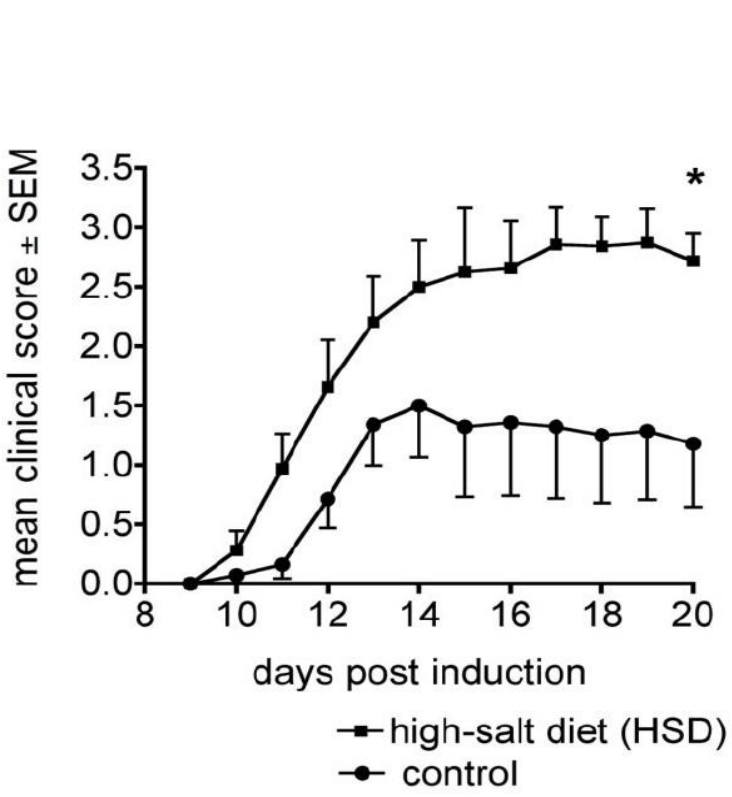
Summary

- Low PUFA intake especially ω-3 is linked to an increased risk for developing MS
- PUFAs can directly act on immune cells and have immunosuppressive effects
- Trials of PUFA supplementation or PUFA-rich diets have had conflicting results and further studies are needed to clarify the role of PUFAs in MS treatment

Salt intake and MS

Salt promotes inflammatory cells and worsens disease in a mouse model of MS





Klienewietfeldt M. et al. Nature. 2013.

Does high salt intake increase MS disease activity ?

Table 2 Association between sodium intake and exacerbation rate in a regression analysis

	IRR	95% CI	p Value
IRR of exacerbation (univariate model)			
Sodium intake (g/day)			
<2	1 (baseline)	–	–
2–4.8	2.56	1.3 to 4.9	0.005
>4.8	3.37	1.5 to 9.55	0.001
IRR of exacerbation (adjusted model)			
Sodium intake (g/day)			
<2	1 (baseline)	–	–
2–4.8	2.75	1.3 to 5.8	0.008
>4.8	3.95	1.4 to 11.2	0.01
Age (1-year increment)	0.992	0.96 to 1.02	0.59
Gender (male)	1.09	0.49 to 2.42	0.82
Disease duration (1-year increment)	0.99	0.98 to 1.01	0.08
Vitamin D (1 ng increase)	1	0.96 to 1.04	0.85
Smoking (smoker)	1.13	0.56 to 2.28	0.73
BMI (1 unit increase)	0.97	0.87 to 1.07	0.58
Treatment (immunosuppressant vs immunomodulators/untreated)	1.46	0.79 to 2.73	0.22

BMI, body mass index; IRR, incidence rate ratio.

Table 3 Association between sodium intake and radiological activity

	IRR	95% CI	p Value
CUA in MRI (univariate model)			
Sodium intake (g/day)			
<2	1 (baseline)	–	–
2–4.8	2.68	1.4 to 4.9	0.002
>4.8	3.56	1.7 to 7.55	0.001
CUA in MRI (adjusted model)			
Sodium intake (g/day)			
<2	1 (baseline)	–	–
2–4.8	2.86	1.52 to 5.4	0.001
>4.8	3.42	1.37 to 8.55	0.008
Age (1-year increment)	0.97	0.93 to 1.00	0.869
Gender (male)	0.57	0.24 to 1.34	0.920
Disease duration (1-year increment)	1.05	0.96 to 1.15	0.25
Vitamin D (1 ng increase)	0.94	0.96 to 1	0.1
Smoking (smoker)	0.51	0.19 to 1.33	0.17
BMI (1 unit increase)	0.92	0.86 to 1	0.06
Treatment (immunosuppressant vs immunomodulators/ untreated)	0.45	0.22 to 1.06	0.06
Average T2 lesion count			
	Mean	SEM	p Value (vs baseline)
Sodium intake (g/day)			
<2	6.45	1.84	–
2–4.8	7.14	0.88	0.743
>4.8	14.13	1.98	0.005

Farez MF et al. J Neurol Neurosurg Psychiatry. 2015.

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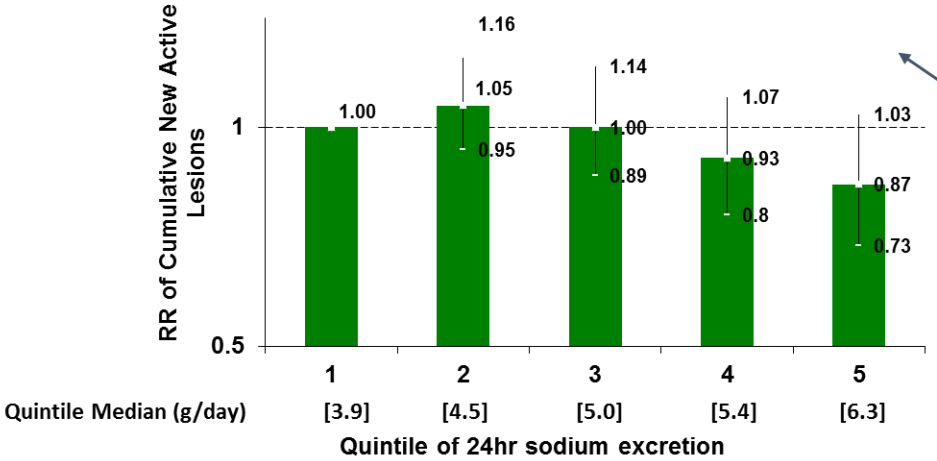
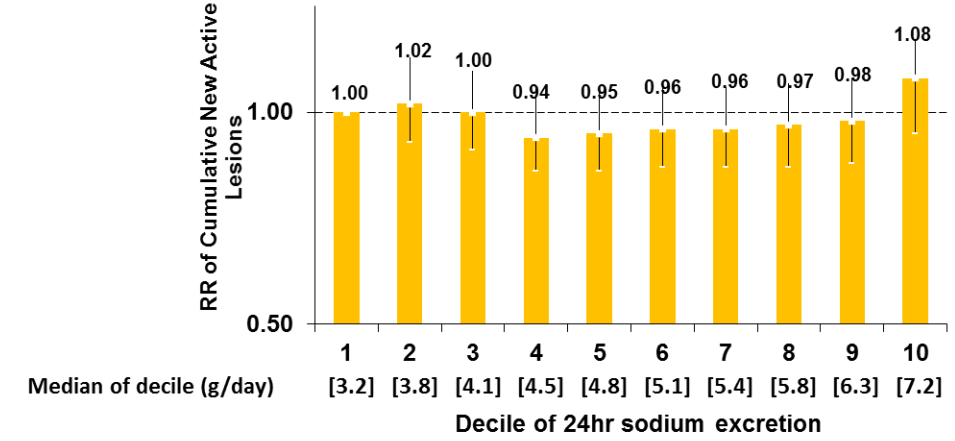
Salt intake does not predict development of new MRI lesions



*Consistent results using quintiles and deciles to assess dose-response



Slide courtesy: Kathryn Fitzgerald ScD

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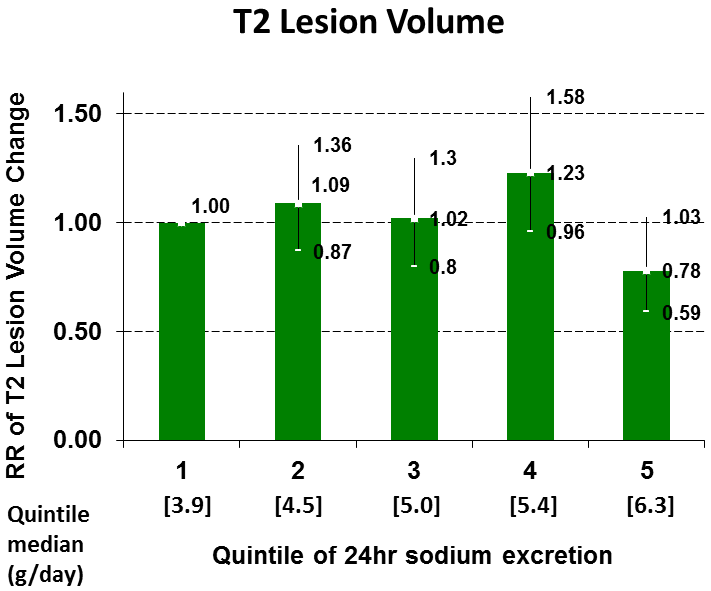
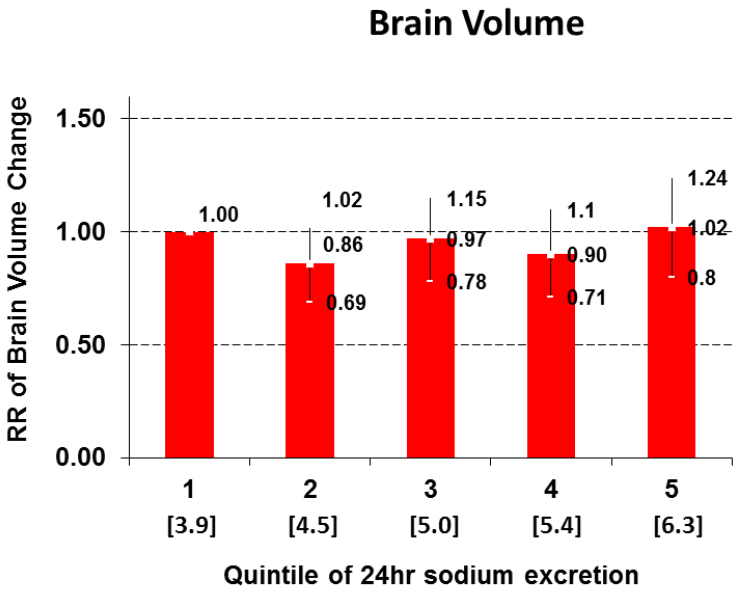
Salt intake does not predict change in T2 lesion and brain volumes





Slide courtesy: Kathryn Fitzgerald ScD

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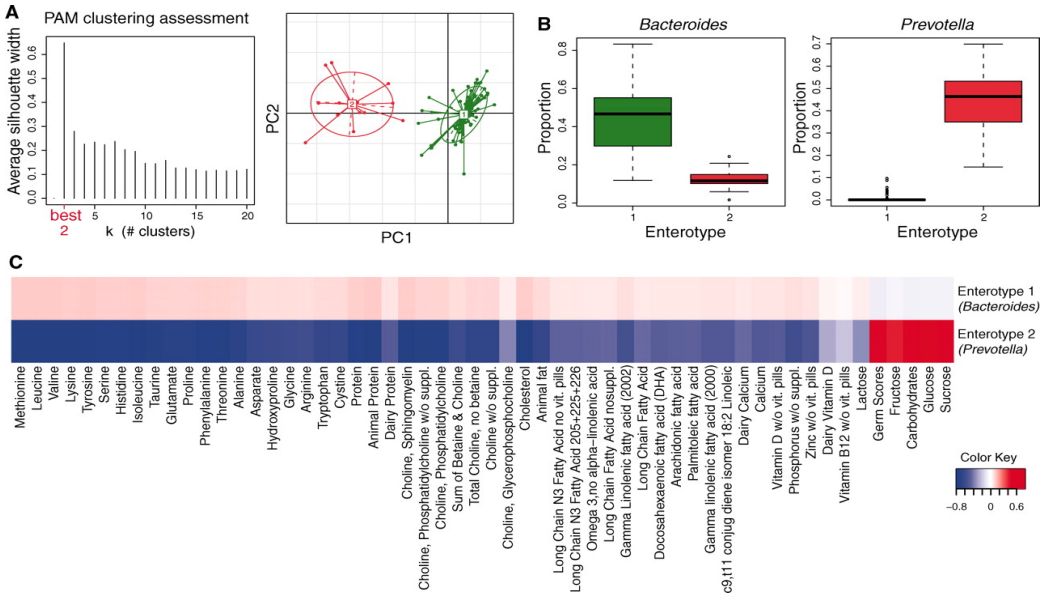
Summary

- High sodium chloride concentrations promote development of inflammatory T cells
- A high-salt diet leads to more severe disease activity in a mouse model of MS
- In a retrospective study there appeared to be increased risk for relapses with increased salt intake
- However, in an analysis of the BENEFIT trial, salt intake appeared to have no relation to clinical or MRI disease activity
- Further studies, including controlled trials are required to clarify the role salt may play in MS

Diets in MS

Long term diet is linked to gut enterotype



Gary D. Wu et al. Science 2011;334:105-108

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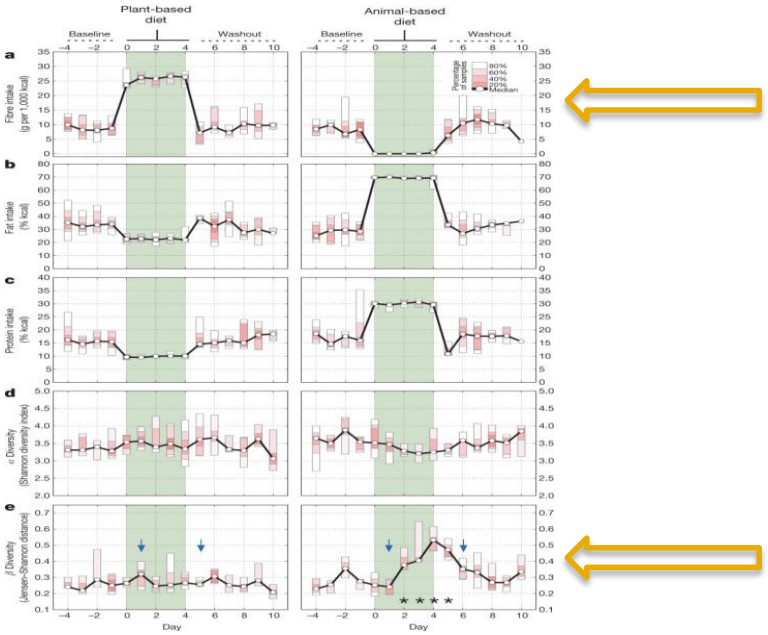
Diet can rapidly alter gut microbiome



LA David *et al. Nature*, 1-5 (2013)

Diets that have been proposed for MS

- Paleolithic diet
- Mediterranean diet
- McDougall diet
- Gluten free diet
- Swank diet

Diets that have good evidence for an effect in MS

Diets that have good evidence for an effect in MS

NONE

Paleo diet

- Attempting to eat a diet – pre-agricultural revolution
- Elimination of processed foods
- Animal protein makes up 30-35% of daily caloric intake
- High fiber intake (45-100 g/day) that is not cereal based
- Low ratio of saturated fats to PUFA

Paleo diet

- Consume 3 servings each/ day of green leafy vegetables, sulfur rich vegetables and intensely colored fruits or vegetables

- Consume 2 tablespoons of omega-3 oils; 4 oz. or more each of animal protein and plant protein; only non-lactose containing milks; no more than 2 servings per week of gluten-free grains/ starchy foods

- Do not consume any dairy or gluten containing grains

Studies on the paleo diet in MS

- One small study of 10 patients of whom 6 completed the study.
- There appeared to be reduction in fatigue scores; however, the diet was coupled with exercise and other interventions.
- The Paleo diet can result in deficiencies in folic acid, thiamine and vitamin B6 (due to reduced intake of cereals), calcium and vitamin D (due to lack of dairy intake) and insufficient caloric intake.

Bisht B et al. J Altern complement Med. 2014.

McDougall Diet

- Low-fat, high carbohydrate, moderate sodium, vegan diet
- Suggested diet staples: wheat flour products, corn, rice, oats, barley, quinoa, potatoes, sweet potatoes, beans, peas, and lentils
- Fresh fruits and non-starch green or colored vegetables
- Low sodium intake encouraged and small amounts of sugar and spices may be used
- No animal-derived foods allowed: dairy, eggs, meat, poultry and fish are excluded. Oils are not allowed (including vegetable oils)

Studies on McDougall diet in MS

- Trial of 61 patients (diet vs wait-listed) – 20% drop-out in diet group,
- Reduction in weight, improved lipid profile and fatigue scores
- No change in MRI and disease parameters
- Diet training was provided in a residential program (10 day)

- The McDougall diet *could* result in deficiencies in iron, vitamin B12, vitamin D, calcium and ω3-fatty acids

Yadav V et al. Mult Scler Relat Disord. 2016.

Mediterranean diet

- Extensively studied for its beneficial effects on cardiac health
- High intake of whole grains, vegetables, fruits, legumes, olive oil and fish
- Low intake of saturated fats (butter and other animal fats), red meat, poultry, dairy products
- Regular but moderate intake of ethanol mainly consisting of red wine during meals

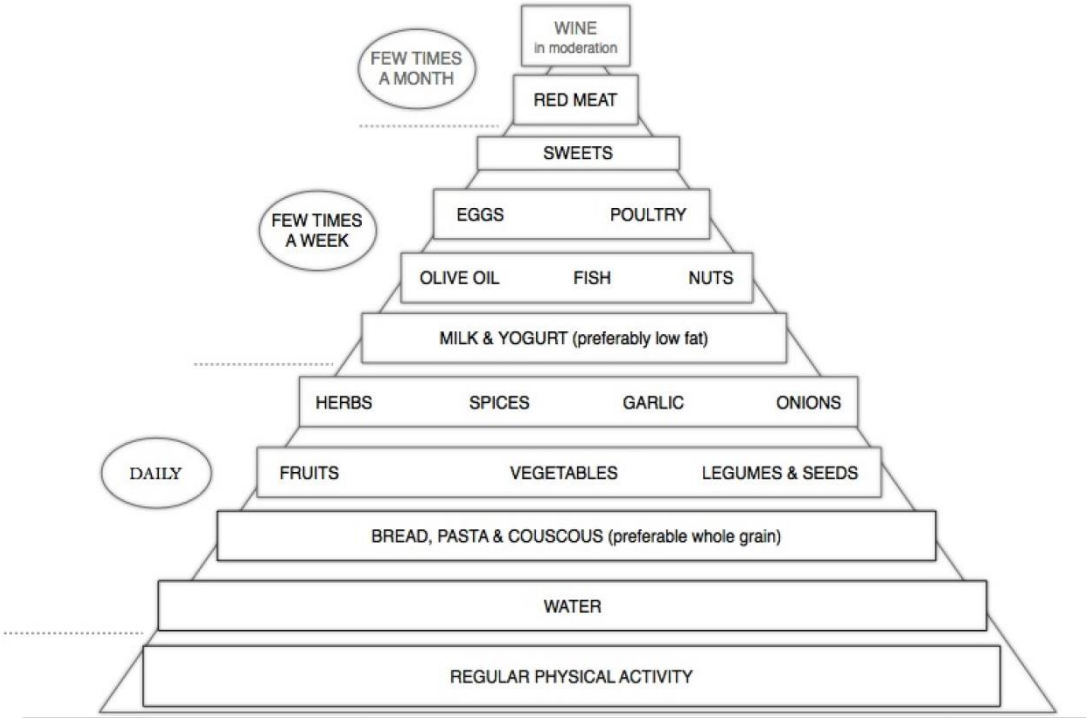


Figure 1: Pyramidal representation of the components of the Mediterranean diet and lifestyle (adapted from Ostan et al.[21])

Swank diet

- Saturated fats < 15 gm/day, while unsaturated fats/ oils < 20-50 gm/day.
- No processed foods containing saturated fats and dairy products < 1% fat.
- Whole grain cereals and pastas are recommended.
- Two cups each of fruits and vegetables are recommended.
- No red meat for the first year after which 3 oz. weekly.
- White fish and shellfish permissible in any amount. Skinned trimmed poultry meat is permissible.
- A cod liver oil and multivitamin supplement recommended.

Studies on Swank diet in MS

- 144 patients followed over 34 years
- Less deterioration and lower death rates in low fat diet compared to high fat diet
- Study conducted prior to introduction of disease modifying therapies
- Lacks appropriate controls

Swank R & Dugan B. Lancet. 1990.

Gluten-free diet

- Gluten is composed of gliadin and glutenin found conjoined with starch in wheat, rye, and barley.
- Major component of the proteins found in wheat.
- Gluten sensitivity is a feature of celiac disease and GFD is a common treatment for this disorder
- “Wheat-free” is not the same as “gluten-free”
- No evidence that this is beneficial in MS patients without gluten sensitivity

What is common to most of the proposed diets for MS ?

Eat food

Not too much

Mostly plants

Michael Pollan

What is common to most of the proposed diets for MS ?

Eat food

Not too much

Mostly plants

Michael Pollan

Does the amount of calories we eat matter ?

- Mouse models of other neurological disorders improved by calorie restriction, with less inflammation in the brain

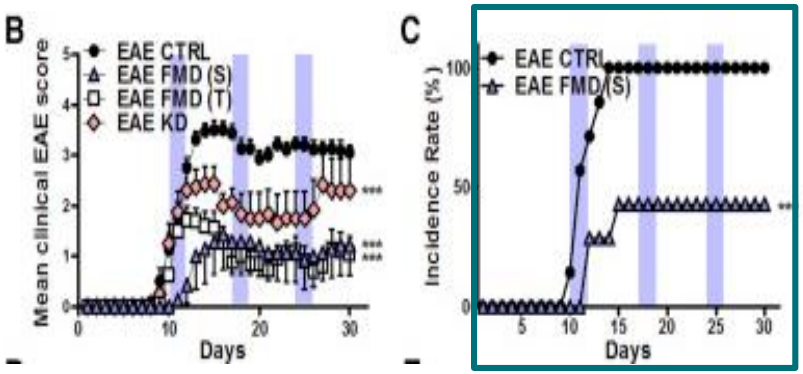
- In mouse models of MS restricting calories or fasting prior to disease induction:

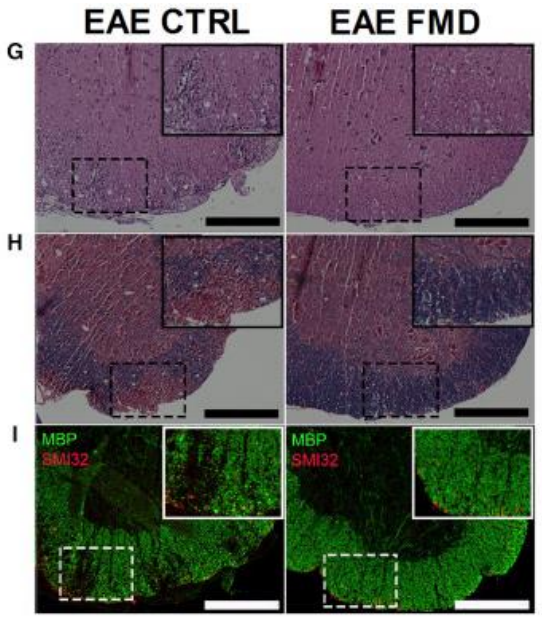
  →Lower risk of disease

  →Less severe disease in the mice that do get it

1. Manzanero S J Cereb Blood Flow Metab 2014
2. Piccio L, J Leukocyte Biology 2008
3. Sanna V, J Clinical Invest 2003

Fasting mimicking diet reduces the severity of a mouse model of MS





Choi IY et al. Cell Rep. 2016.

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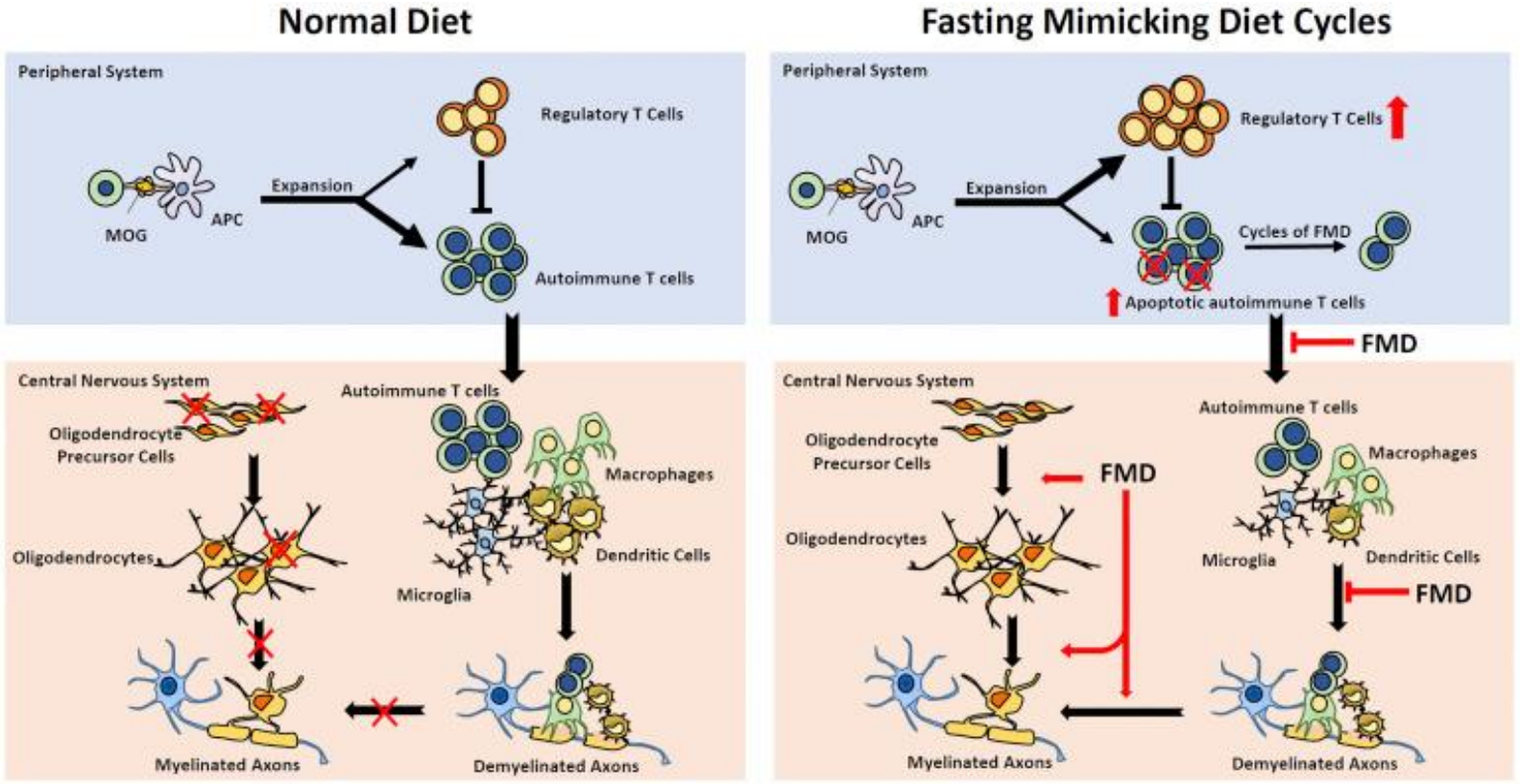
Caloric restriction and the immune system



Choi IY et al. Cell Rep. 2016.

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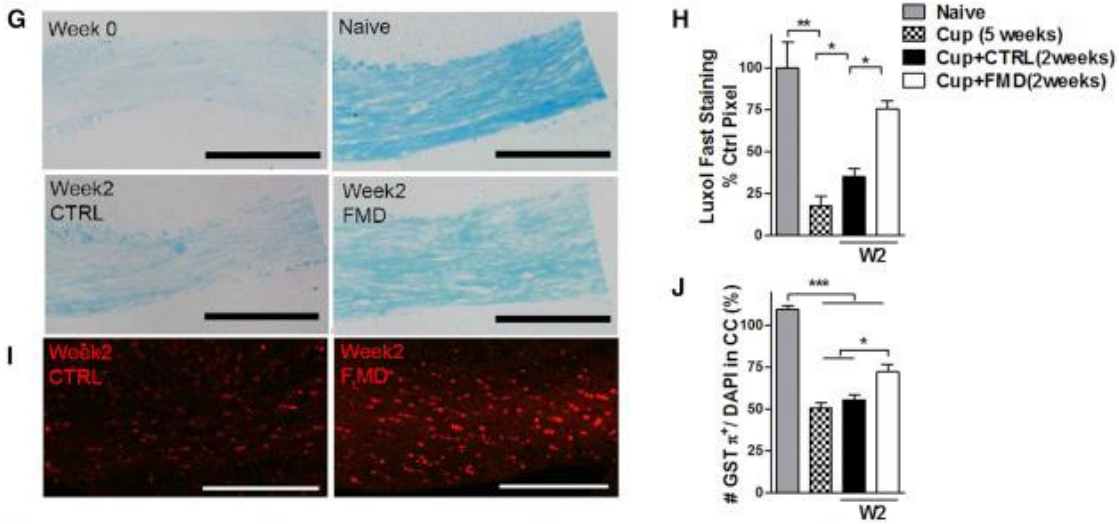
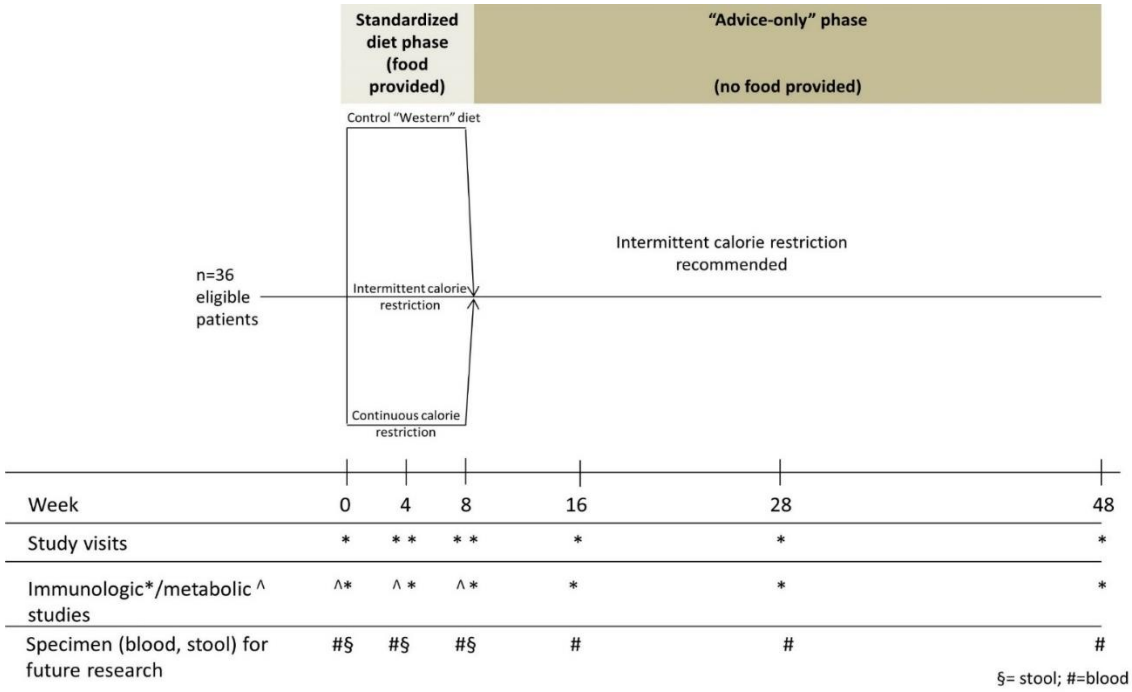
Caloric restriction may promote remyelination in a mouse model



Choi IY et al. Cell Rep. 2016.

Intermittent caloric restriction trial



Slide courtesy: Ellen M. Mowry, MD, MCR. Johns Hopkins University

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Summary

- Various diets have been proposed for MS, but evidence for a clear benefit for any of them is lacking
- Rigorous studies that include measures of adherence, disease activity, and quality of life are required
- Caloric restriction or fasting appears to lead to reduction of inflammation and perhaps promotes repair in mouse models
- Trials of fasting diets are ongoing and will provide more information on the feasibility and efficacy of this intervention

Future directions for Diet in MS

- There is a need to study diet and supplements in MS
- Currently insufficient high-quality data to recommend a specific diet or supplement for the treatment/ prevention of MS
- Though studies are challenging to do, they are necessary in the light of prior experience with other supplements

Questions/Comments

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Can Do MS Resources

e|NEWS
your best life update

Q&A

Can Do Library

http://www.mscando.org/living-with-multiple-sclerosis/can-do-library/ms-education/diet-and-multiple-sclerosis

Find these resources and more at www.MSCanDo.org

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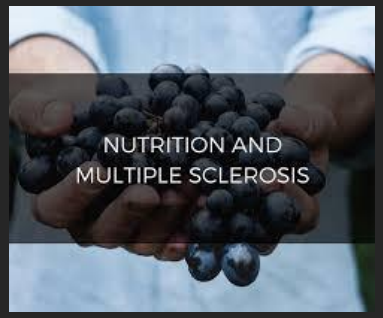
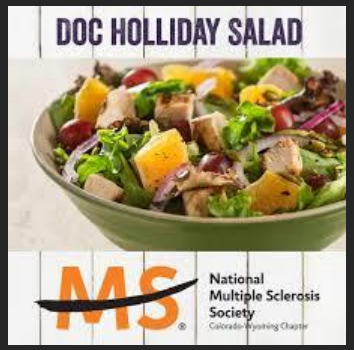
National MS Society Resources



[Nutrition and MS]



[The Power Pantry]

[Food for Thought – MS and Nutrition]

MS
National
Multiple Sclerosis
Society

Our Mission:

People affected by MS can live their best lives as we stop MS in its tracks, restore what has been lost and end MS forever.

[NationalMSSociety.org/Diet]

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Sleep in MS:
Strategies for Improving Your Zzz's

December 13, 2016

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